Synthesis of Protease Inhibitors Targeting the 20S Proteasome and SARS-CoV-2 Main Protease

Research Thesis

Presented in partial fulfillment of the requirements for graduation with research distinction in Chemistry* in the undergraduate colleges of The Ohio State University

by

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Abstract

Proteases are enzymes that regulate the hydrolysis of peptide bonds via a process called proteolysis.[1] They are essential for many diverse processes including processing protein activity and interactions, digestion, blood clotting, host defense, pathogenic infection, viral replication, wound healing, disease progression, and they also generate, transduce, and amplify chemical signals.[2] The proteases' functions give them a key role in DNA replication and transcription, allowing them to control cell replication and death.[2] Specific proteases have become targets in many diseases such as cancer, neurological disorders, viral infections, inflammation, and arthritis.[3] Inhibitors of proteases have become of interest as treatment options because they stop proteolysis, thus causing the diseased cell to die. One such target protease is the proteasome for the treatment of multiple myeloma. However, current approved proteasome inhibitor drugs are not specific enough and cause serious side effects to patients, urging the development of new more selective inhibitors.[12] In this thesis, we present the synthesis of novel Michael acceptor inhibitors for the eukaryotic protease that is abundant in multiple myeloma cells, the 26 proteasome, and the main protease of corona viruses, the M_{pro}.[22]

Acknowledgments

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Abbreviations

μM	micromolar
13B	peptidomimetic α-ketoamide inhibitor
Å	angstrom
AcOH	acetic acid
Ala	alanine
ALeu	aza-leucine
Boc	tert-butyloxycarbonyl group
C-L	caspase-like
Cbz	carboxybenzyl group
CT-L	chymotrypsin-like
Cys	cysteine
DCM	dichloromethane
diH_2O	distilled water
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
FDA	food and drug administration
Fmoc	fluorenylmethoxycarbonyl protecting group
Gln	glutamine
HBtu	hexafluorophosphate benzotriazole tetramethyl uronium

HCl	hydrochloric acid
HOBt	hydroxybenzotriazole
HPh	homophenylalanine
hr	hour
iBCF	isobutylchloroformate
IgA	immunoglobulin A
IgG	immunoglobulin G
Leu	leucine
M	molar
MeOH	methanol
MERS	Middle Eastern respiratory syndrome
mg	milligram
min	minute
mmol	millimolar
Mp	morpholine group
M_{pro}	coronavirus main protease
MS	Mass spectroscophy
N3	broad spectrum Michael acceptor 3C protease inhibitor
Na_2SO_4	sodium sulfate
$NaCNBH_3$	sodium cyanoboro hydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
NMM	*N*-methylmorpholine

NMR	nuclear magnetic resonance
P_1	amino acid 1
P_2	amino acid 2
P_3	amino acid 3
Ph	phenyl group
Phe	phenylalanine
PyBop	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RNA	ribonucleic acid
RT	room temperature
S_1	subsite 1
S_2	subsite 2
S_3	subsite 3
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
T-L	trypsin-like
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thr	threonine
Tyr	tyrosine
Val	valine

Chapter 1: Introduction

1.1: Proteases as Targets for Disease Treatment

Proteases are essential enzymes that regulate the hydrolysis of peptide bonds via a process called proteolysis.[1] There are 460 different proteases in humans, placing them as the second largest enzyme family following the ubiquitin ligases.[1] They are involved in processing protein activity, protein interactions, cellular information, digestion, blood clotting, pathogenic infection, and generate, transduce, and amplify chemical signals.[2] Thus, proteases play a key role in DNA replication and transcription, allowing them to control cell replication and death.[2] A defect in proteases function can lead to development of diseases such as cancer, neurological disorders, viral infections, inflammation, and arthritis.[3] To treat diseases caused by damaged proteases, inhibitors of the protease have been developed and sought after. The challenge is to create a protease inhibitor with a structure that is highly selective for the desired protease only. Proteases are characterized into seven classes based on their active site residue that catalyze substrate cleavage, and into clans based on their structure and fold.[1] The seven classes include aspartic, cysteine, glutamic, metallo, serine, and threonine peptidases, and asparagine peptide lyase.[4]

The target protease in Dr. Ekici's research project is the 26S proteasome, which is part of the threonine peptidase class. It is found distributed throughout extracellular and intercellular space of cells and is essential in eukaryotic cells for protein degradation and quality control of newly synthesized proteins via the ubiquitin-proteasome pathway.[1, 5, 7] Protein degradation is vital for the survival of cells because it removes toxic misfolded proteins and provides nutrition by recycling amino acids during starvation conditions.[6] The proteasome was initially a target for anti-inflammatory agents, however after further research, it was discovered that proteasome inhibitors cause apoptosis of different cancer cells, more specifically multiple myeloma.[7] It was also

discovered that inhibitors were selective to diseased cell, reducing concerns of high toxicity due to interference with protein quality control of healthy cells.[7] Multiple myeloma cells synthesize a large amount of IgG and IgA protein.[7, 8, 9] Misfolded IgG proteins are cleaved by proteasomes via the endoplasmic reticulum degradation pathway, therefore multiple myeloma cells require a unusually large amounts of proteasomes to be present in the cell.[7] This increases the sensitivity of multiple myeloma cells and makes them great targets for proteasome inhibitors.[7, 10] There are currently three FDA approved drugs, bortezomib (2003), carfilzomib (2012), and Ixazomib (2015) for the treatment of multiple myeloma **(Figure 1**).[12] Unfortunately, these drugs cause serious side effects like peripheral neuropathy (bortezomib and ixazomib), or cardiovascular adverse effects (carfilzomib).[12] With the intent to reduce these side effects, a new, more specific proteasome inhibitor must be developed.

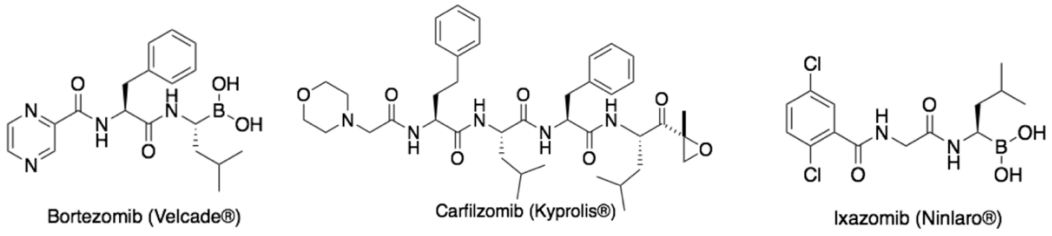


Figure 1. FDA approved proteasome inhibitors

1.2: The 26S Ubiquitin-Proteasome Pathway

The 26S ubiquitin-proteasome pathway allows for the proteasome to recognize peptides and receive them for proteolysis **(Figure 2)**. The 26S proteasome barrel shaped and is made up of three subunits: the 20S proteolytic core and two 19S regulatory particles.[7] The ubiquitin enzyme labels proteins intended for degradation. The 19S regulatory particles of the proteasome recognize the labeled proteins and allows them to enter the proteasome in preparation for proteolysis.[7] The protein then enters the complex four-ring hollow cylindrical structure of the 20S core, which is

made of two outer α rings and two inner β rings.[7] The β rings contain the catalytic residues responsible for proteolytic activity: β1 caspase-like (C-L), β2 trypsin-like (T-L) and β5 chymotrypsin-like (CT-L).[7]

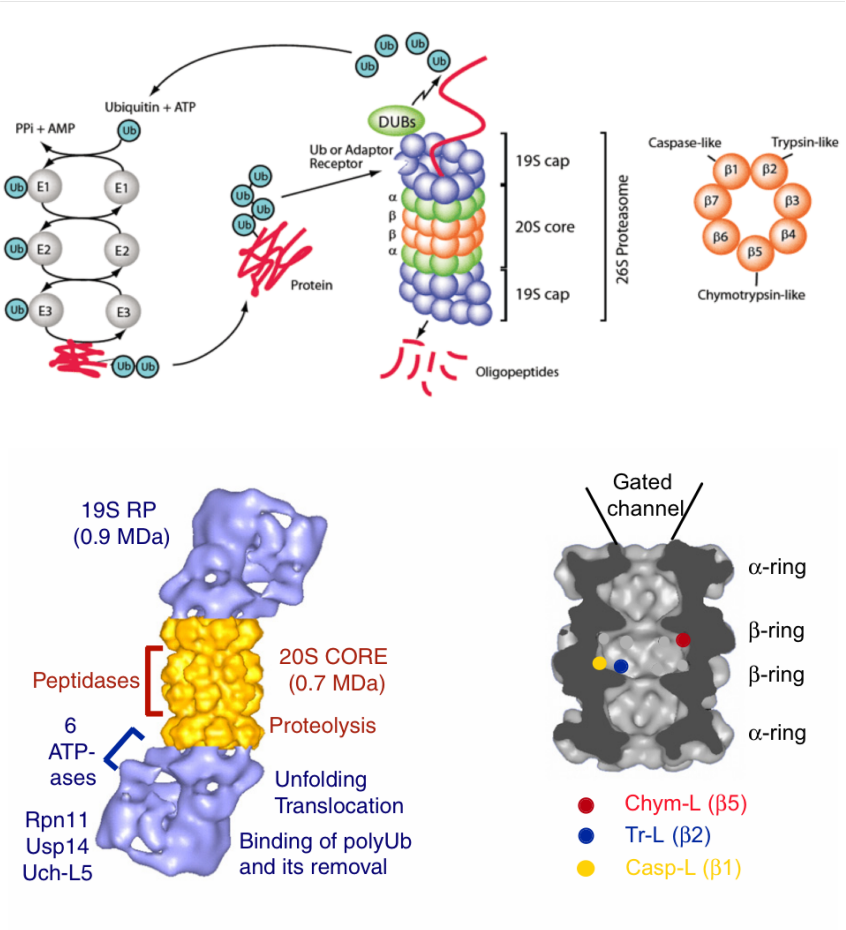
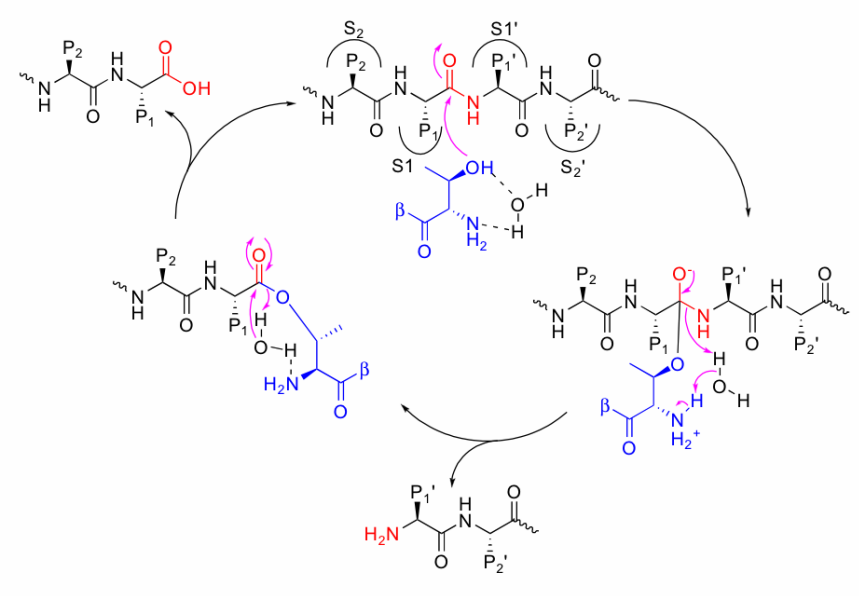


Figure 2. 26S ubiquitin-proteasome pathway and active sites.[7]

The active cites cleave peptide bonds by the hydroxyl group of the N-terminal threonine acting as a nucleophile (Mechanism 1).[7, 13] The β1 C-L inactivation via inhibition of the catalytic threonine showed no phenotypic defects and no substrate accumulation inside the cell.[7, 14] The β2 T-L inhibition somewhat decreased growth and degradation of some substrates.[7, 14, 16] The inhibition of the β5 CT-L is the most significant, as it substantially reduced growth, increased production of

misfolded proteins, and caused a buildup of proteasome substrates in the cell.[15, 16] Thus, the target is the β5 CT-L active site to shut down the function of the proteasome and lead to apoptosis.



Scheme 1: General mechanism of inhibition of the threonine residue[7]

1.3: Nomenclature

To effectively inhibit the function of the 26S proteasome, a peptide sequence that is highly selective for the CT-L active site of the 20S core must be synthesized. The ideal peptide sequence has been studied to have a Leu amino acid residue at the P3 position to sit in the S3 position of the active site.[18] It has also been researched that selectivity is enhanced with a bulky group/structure at the P2 position for the S2 of the active site.[17, 18] The S1 position has also been studied to prefer a Leu, Phe, or Tyr residue.[18]

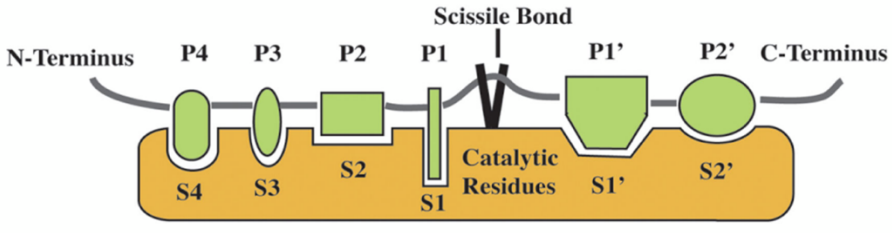
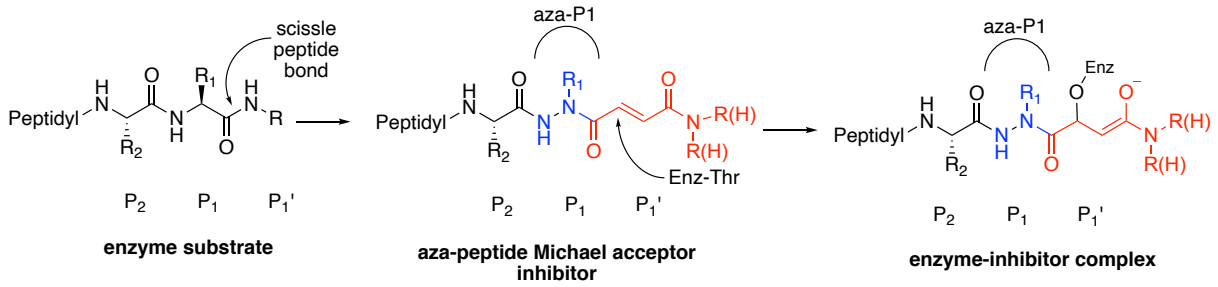


Figure 3: Active site map of proteases[19]

1.4: Inhibitor design

Our inhibitor design is an ideal peptide sequence that has high affinity for the active site residues and is attached to an electrophilic chemical warhead. Our warhead design consists of a Michael acceptor group that is proposed to react with the proteasome's active site nucleophilic threonine oxygen to form a covalent bond **(Scheme 2)**. This covalent modification is expected to be irreversible resulting in also so-called suicide inhibition.[19] It takes advantage of the enzymes catalytic machinery to shut down the enzymes function completely.[19] The peptide design has an achiral P1 aza-leucine residue aimed to limit the off-target protease activity, it is also corresponding to preferred proteasome substrate preference to ensure selectivity.[18]

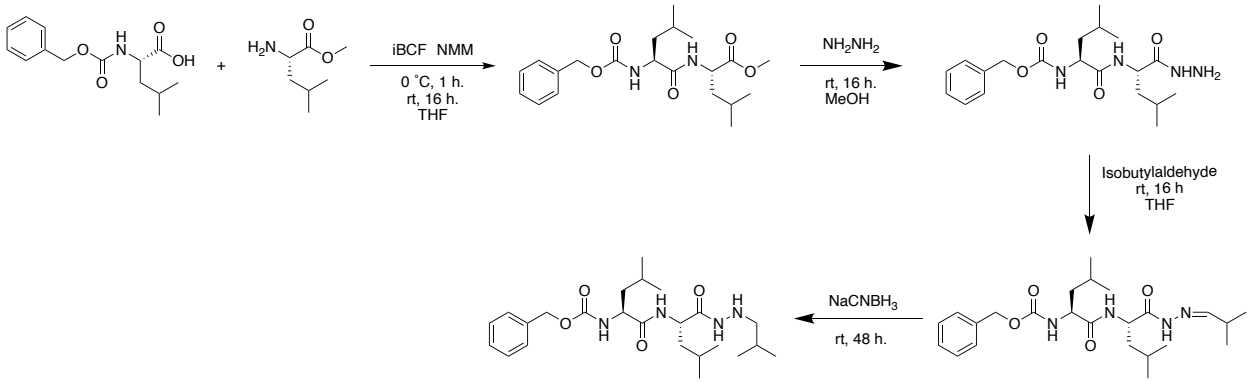


Scheme 2: Proposed mechanism of inhibition of the 20S Proteasome by a Michael acceptor inhibitor

1.5: Synthesis strategy

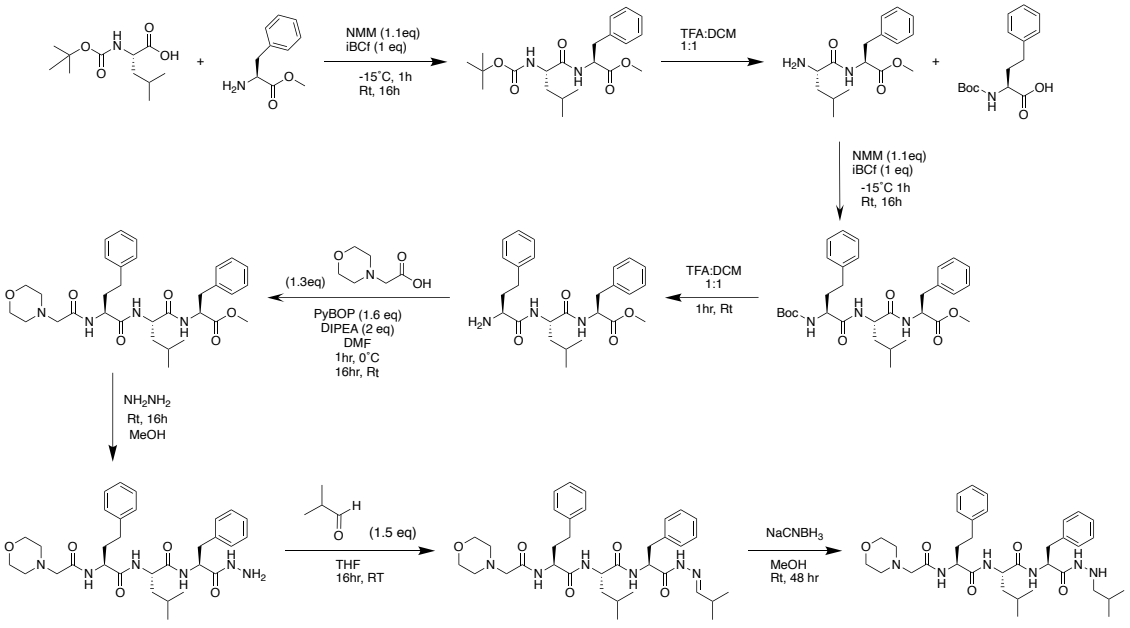
The synthesis of the Michael Acceptor Inhibitors begins with the peptide backbone. A variety of different peptide backbones were synthesized to find the most effective inhibitor. The sequence of each tri- and tetrapeptide begins with a protecting group (Pg) followed by amino acid residues that dock into the active site positions. The first step in the synthesis of the peptide back bone involves the coupling of Pg-AA_1-OH to H-AA_2-OMe using a general coupling method that utilized NMM and *i*BCF. Next, hydrazine is used to create the hydrazide, followed by a two-step reductive

amination using isobutryaldehyde and $NaCNBH_3$. A general synthesis scheme of the tripeptide Cbz-Leu-Leu-ALeu sequence precursor is shown in Scheme 3.



Scheme 3: Synthesis of Cbz-Leu-Leu-ALeu precursor

To synthesize the tetrapeptides, a deprotection and additional coupling step is needed to add another amino acid to the peptide sequence. The peptide synthesis of the tetrapeptides begins with a Boc protecting group that is removed using 1:1 volume of TFA and DCM to allow for the coupling of an additional amino acid and protecting group. The synthesis of the tetrapeptide precursor Mp-Phe-Leu-Phe-ALeu is shown in **Scheme 4**.



Scheme 4: Synthesis of tetrapeptide Mp-Phe-Leu-Phe-ALeu precursor.

The precursor sequences synthesized using the general peptide synthesis methods include: Mp-Phe-Leu-Phe-ALeu, Cbz-Hph-Leu-Phe-ALeu, Cbz-Leu-Leu-ALeu, and Cbz-Leu-Phe-ALeu **(Figure 4)**.

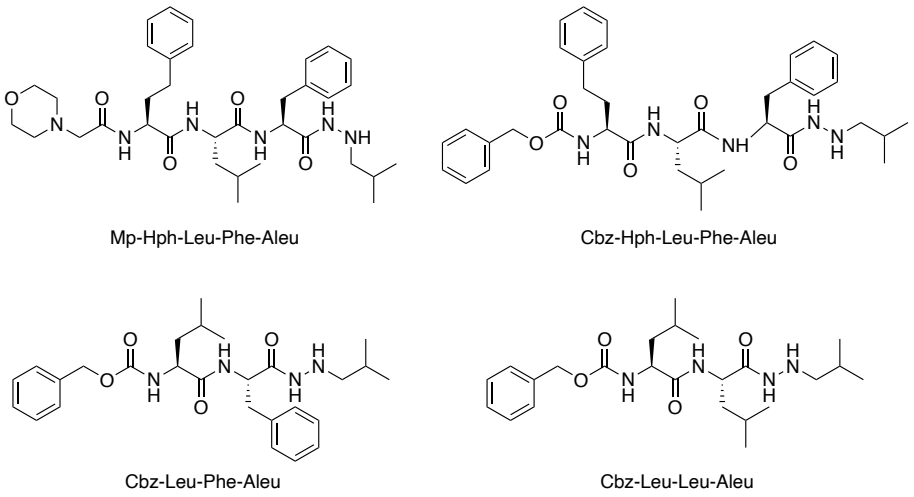
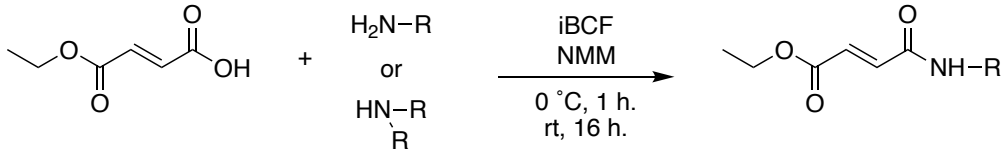


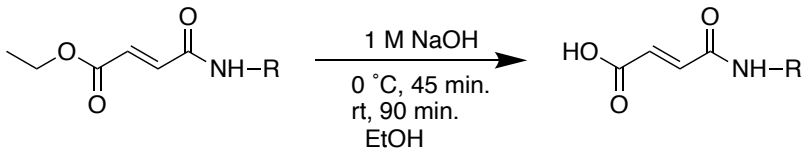
Figure 4: Synthesized Peptide backbone sequences.

Next, a two-step method was used to synthesize the Michael acceptor warheads. The first step was a coupling of monoethyl fumarate to the desired amine using NMM and *i*BCF **(Scheme 5)**.



Scheme 5: Monoethyl fumarate coupling to amine.

Step 2 involved the hydrolysis of the ethyl ester group to produce the warhead that is ready to couple to the peptide backbone **(Scheme 6)**.



Scheme 6: Hydrolysis of the ethyl ester to produce the Michael Acceptor warhead.

A variety of Michael acceptor warheads were synthesized to determine the best compound to react with the proteasome's active site threonine residue. All synthesized warheads are shown in **Figure 6** (Note that the benzylamide fumaric acid was synthesized by Ms. Kayla Kucway).

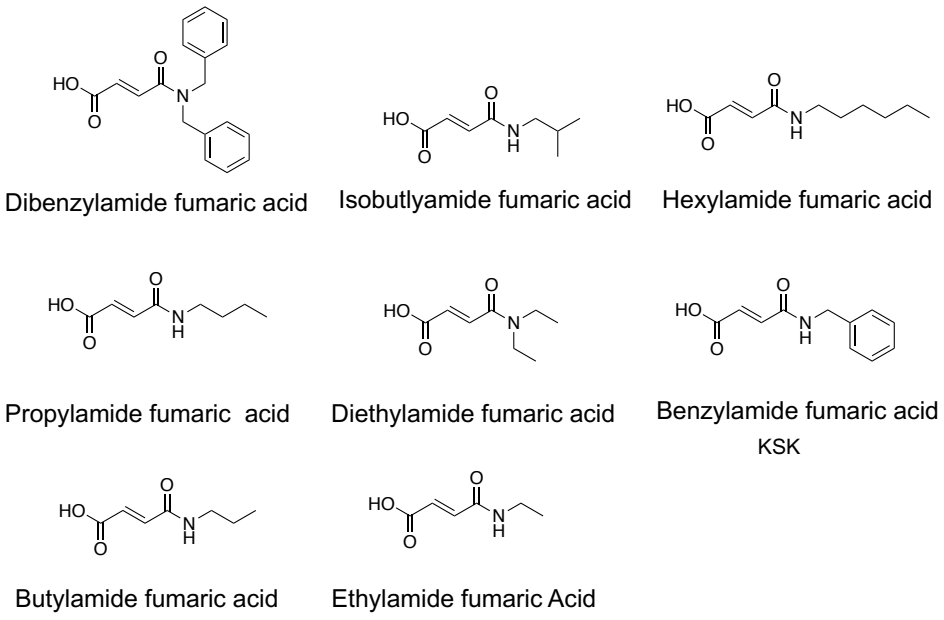
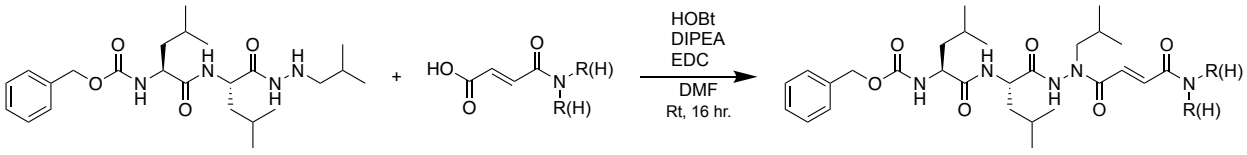


Figure 5: All synthesized Michael acceptor warheads.

The final step in the inhibitor synthesis was the coupling of the peptide backbone to the Michael acceptor warhead, which involved the use of EDC, HOBt, and DIPEA. A general coupling of a warhead with the Cbz-Leu-Leu-ALeu precursor is shown is **Scheme 7**. Many final aza-peptide Michael acceptor inhibitors were also synthesized by Ms. Leilani Lotti Diaz and Dr. Sarah Border.



Scheme 7: Coupling of the peptide backbone to the Michael acceptor warhead.

1.6 : Inhibition of the Human 20S proteasome by Aza-peptide Michael Acceptor Warheads

The synthesized aza-peptide Michael acceptor warheads inhibition ability was evaluated *in vitro* by Dr. Sarah Border, and Prof. Ozlem Dogan Ekici. The kinetics data collected displayed in **Table 1.**

Inhibitor	**IC_{50} (μM)**
Cbz-Leu-Leu-ALeu-CH=CH-COOEt	3.7 ± 2.6
Cbz-Leu-Leu-Aleu-CH=CH-CONHEt	5.5 ± 1.2
Cbz-Leu-Leu-ALeu-CH=CH-COOBn	13.8 ± 7.3
Cbz-Leu-Leu-ALeu-CH=CH-CONHBn	0.94 ± 0.2
Cbz-Leu-Leu-ALeu-CH=CH-$CONBn_2$	1.3 ± 1.1
Cbz-Leu-Leu-ALeu-CH=CH-CONH-iBu	2.0 ± 0.4
Cbz-Hph-Leu-Phe-ALeu-CH=CH-COOBn	0.92 ± 0.3
Cbz-HPh-Leu-Phe-ALeu-CH=CH-CONHEt	3.1 ± 1.5
Cbz-HPh-Leu-Phe-ALeu-CH=CH-CONHBn	11.2 ± 4.2
Mp-Hph-Leu-Phe-ALeu-CH=CH-COOEt	5.7 ± 2.5
Mp-HPh-Leu-Phe-ALeu-CH=CH-CONHBn	0.21 ± 0.05*

Table 1: *InVitro* Inhibition Data of 20S Proteasome with Aza-peptice Michael Acceptor Inhibitors

The aza-peptide Michael acceptors displayed low μM-range inhibition of the human 20S proteasome. From the kinetic data it can be concluded that the tetrapeptidyl inhibitors are more potent than the tripeptidyl inhibitors and the best compound is the tetrapeptide Mp-HPh-Leu-Phe-ALeu-CH=CH-CONHBn with IC_{50} = 0.21 μM. Comparing this value to the Cbz-HPh-Leu-Phe-ALeu-CH=CH-CONHBn IC_{50} of 11.2 μM, it is observed that the morpholine group improves potency approximately 50-fold.

Chapter 2: SARS-CoV-2 Main Protease Inhibitors

2.1: SARS-CoV-2 Introduction

Over the past two decades, the coronavirus has caused three large-scale outbreaks: severe acute respiratory syndrome (SARS) in 2003, Middle Eastern respiratory syndrome (MERS) in 2012, and now severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019.[21] To date, the novel coronavirus SARS-CoV-2 has affected 251 million people worldwide and caused over 5 million deaths.[27] The COVID-19 pandemic caused by SARS-CoV-2 spiked panic across the world and urged for the development of treatments or vaccines. Due to SARS-CoV-2's ability to spread so quickly, the world raced to create a vaccine to control infection rate. As of today, there are over 20 SARS-CoV-2 vaccines developed between the United States and other countries. The vaccines developed include viral vector, inactivated, RNA, protein subunit, and DNA vaccines. These vaccines, particularly the mRNA vaccines, have been proven highly effective. Data so far indicates that booster shots may require annually.

The main concern for a mutation site is the SARS-CoV-2 spike protein, which mediates the virus entry into the host cells.[20] With the emergence of new variants of SARS-CoV-2, and the unpredictability of the mutation sites, future coronavirus outbreaks are possible. Therefore, it is crucial to develop new therapeutics that can target and affect all variants of the virus. To be able to treat all novel coronavirus cases post-infection, the main protease of SARS-CoV-2, the $M_{pro,}$ has emerged as the best target for treatment. SARS-CoV-2 M_{pro} is essential for survival of the virus and does not mutate between variants.[22, 23] The M_{pro} structure is conserved between all coronaviruses and mutations to the protease are lethal to the virus.[22] Thus, the M_{pro} is an excellent target for new therapeutic inhibitors to treat SARS-CoV-2 and other future coronavirus variants. Based off a research report published by A. Shirit, the key interactions of SARS-CoV and SARS-

CoV-2 main proteases are conserved.[24] Utilizing this information and the revealed X-ray crystal structure (PDB ID: 6LU7), Dr. Ozlem Dogan Ekici has proposed novel inhibitor structures designed specifically for the SARS-CoV-2 M_{pro} to inhibit the virus' replication.

2.2: Preliminary Data

The SARS-CoV-2 M_{pro} is a cysteine protease with preference for the tetrapeptide sequence Ala-Val-Leu-Gln.[23] 144 inhibitors were designed and proposed to be suicide inhibitors that aim to alkylate the active site of the M_{pro}. More specifically, the inhibitor's electrophilic warhead is expected to react with the nucleophilic cysteinyl sulfur atom of the SARS-CoV-2 M_{pro} to form a covalent bond, thus inhibiting the protease's function and prohibiting replication. The novel inhibitors energetic scores for the docked poses were compared to determine the best inhibitor design **(Figure 6)** by Dr. William Coldren. The docking score of a known broad spectrum Michael acceptor 3C protease (old name for M_{pro}) inhibitor **(red dot, Figure 6)**, N3, and a newly published peptidomimetic α-ketoamide inhibitor **(yellow dot, Figure 6)**, 13B, were used as reference points. From the docking scores, it was concluded that 23 of the proposed designs have better docking scores (more negative) than the reference inhibitor, N3, and of those 23, 15 performed better than 13B. Also, to compare inhibitory activity, the Tanimoto similarity scores of the novel designs were also compared to the reference compound N3. The top 23 compounds all received a score of 0.75 and higher, suggesting they will inhibit the SARS-CoV-2 M_{pro}. A molecular dynamics simulation was also conducted for the top performing compound and the results gave a RMSD value less than 2.5 Å, suggesting excellent binding with the M_{pro}.

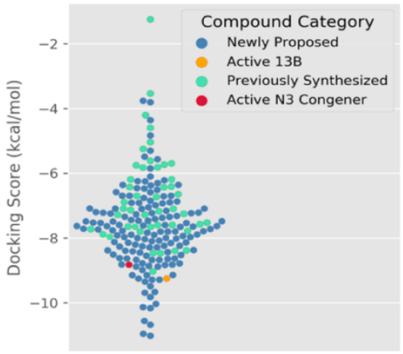


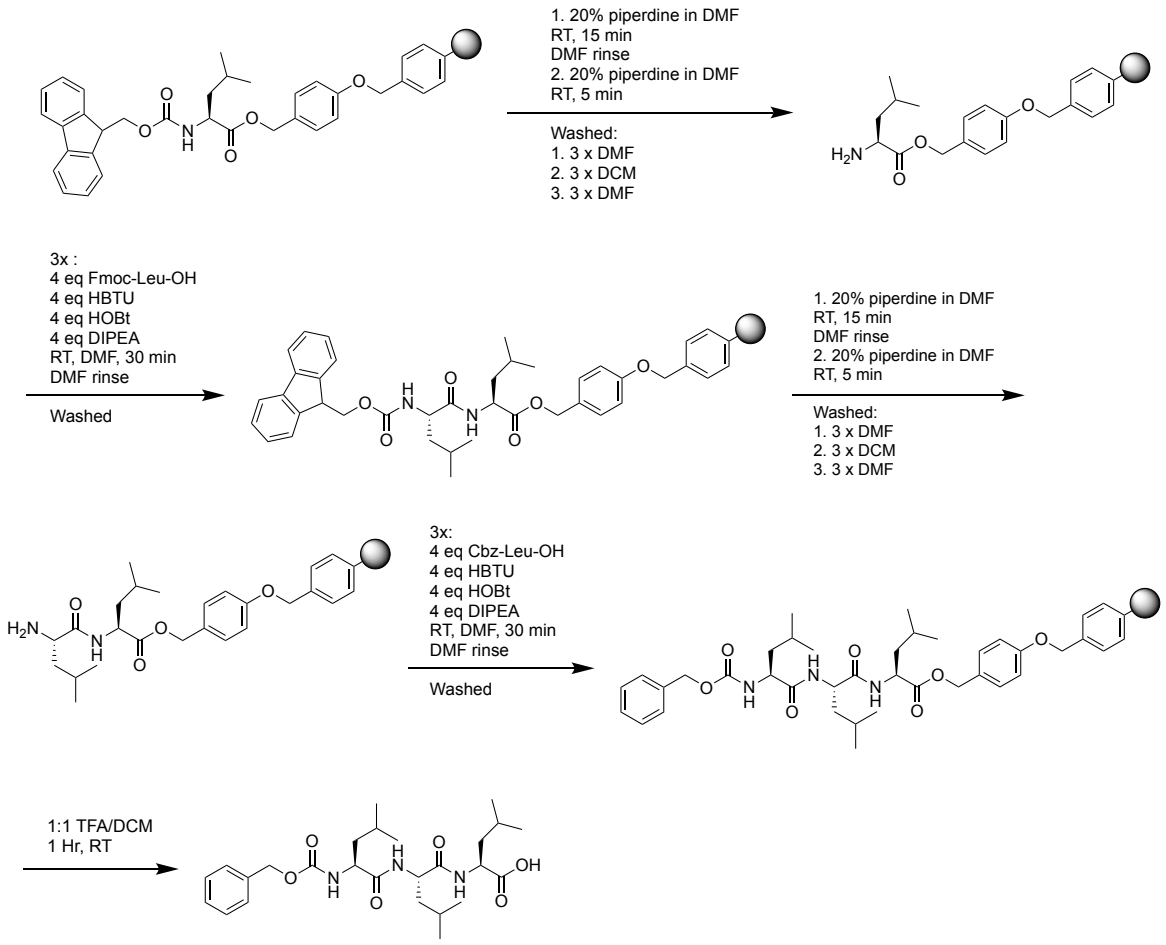
Figure 6: Docking scores of 144 novel inhibitor designs compared to N3 (red dot) and 13B (yellow).

2.3 Inhibitor Design

The inhibitor designs consist of tri- and tetrapeptidyl frameworks with a protecting group and an electrophilic warhead. Investigators at Pfizer have discovered the M_{pro} has a strong preference for inhibitors with a Gln at the P1 position, small hydrophobic residues at the P2 and P4 position, and a 2-pyridone group embedded in the compounds structure.[25, 26] As for the warhead, the best performing inhibitors based on preliminary data in our above-mentioned studies were obtained with epoxides and ketone warheads. Using this information, a framework of proposed inhibitors was designed to be synthesized.

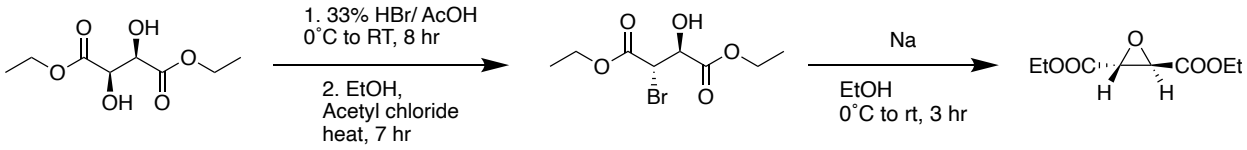
2.4: Synthesis Strategy

To optimize time and synthetic effort, a solid-phase based approach is followed to synthesize the peptide backbones. A general procedure for the solid-phase synthesis method of the peptide backbone is shown in **Scheme 8** to synthesize Cbz-Leu-Leu-Leu-OH. The preferred peptide sequence for SARS-CoV-2 M_{pro} is Ala-Val-Leu-Gln, which will be also synthesized via solid-phase peptide synthesis similar to as outlined in Scheme 8.

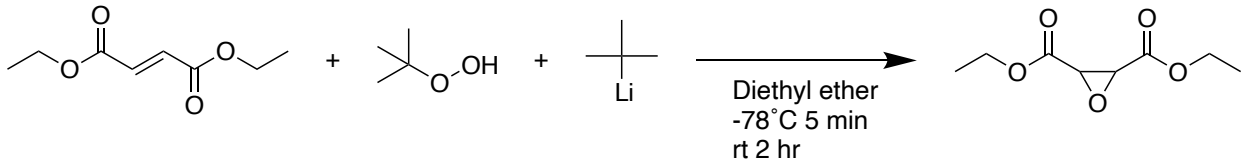


Scheme 8: Solid phase synthesis of Cbz-Leu-Leu-Leu-OH

To synthesize one of the proposed warheads, the epoxide warhead, for the SARS-CoV-2 inhibitors, two different methods were attempted. The first method involved the synthesis of the *R,R* or *S,S* epoxide starting from L- or D-diethyl tartrate, respectively **(Scheme 9)**. This approach involved a two-step substitution with bromine, followed by an epoxidation step using Na. The second method involved reacting diethyl fumarate with *tert*-butyl lithium and *tert*-butyl hydroperoxide to produce a *trans* epoxide **(Scheme 10).** Studies are ongoing in Dr. Ekici's laboratory to optimize the conditions for these two syntheses. Once these warheads are synthesized, the peptide backbone will be coupled to the epoxide warhead in the final step of the SARS-CoV-2 M_{pro} inhibitor synthesis**.**



Scheme 9: *R,R* epoxide synthesis from diethyl-L-(+)-tartrate.



Scheme 10: *Trans* epoxide synthesis.

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Experimental

Procedures for synthesized compounds

General NMM and *i*BCF Coupling Procedure:

Two oven-dried round bottom flasks were utilized and labeled as flasks A and B. To flask A was added Pg-AA1-COOH (10 mmols, 1 eq) in dry THF (100 mL) and brought to -15˚C. To flask B was added H-AA2-OMe (10 mmols, 1 eq) in dry THF (100 mL) and brought to -15˚C. NMM (11 mmols, 1.1 eq) was added to flask A dropwise via syringe and left to react for 10 minutes. Once the 10 minutes elapsed, *i*BCF (10 mmols, 1 eq) was added to flask A and allowed to react for 30 minutes. 15 minutes into the *i*BCF reaction, NMM (11 mmols, 1.1 eq.) was added to flask B and left to react for 15 minutes. Flask B was then added to flask A and left to stir at -15˚C for 1 hour, then allowed to warm to room temperature to react overnight. The reaction was then concentrated under reduced pressure. The residue was treated with EtOAc (100 mL) and diH_2O (100 mL). The organic layer was washed 3x with 1 M HCl (100 mL), saturated $NaHCO_3$ (100 mL), brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

Formation of hydrazide procedure:

A solution of Pg-AA_1-AA_2-OMe (16 mmols, 1 eq) in MeOH (50 mL) was treated with excess hydrazine (160 mmols, 10 eq) and allowed to react for 16 hours at room temperature. MeOH and hydrazine were removed under reduced pressure.

Reductive Amination Procedure – Step 1:

A solution of Pg-AA_1-AA_2-$NHNH_2$ (15 mmols, 1eq) was dissolved in dry THF (100 mL)and treated with isobutyraldehyde (22.5 mmols, 1.5 eq) dropwise at room temperature. The reaction

mixture was left to stir for 16 hours. Solvent was removed under reduced pressure and crude was purified using flash column chromatography (10% MeOH/ DCM).

Reductive Amination Procedure – Step 2 ($NaCNBH_3$ Reduction):

Pg-AA_1-AA_2-NHNCHCH$(CH_3)_2$ (15 mmols, 1 eq) was dissolved in MeOH (100 mL) at room temperature. $NaCNBH_3$ (60 mmols, 4 eq) was added to the solution followed by dropwise addition of Acetic acid via syringe and allowed to react for 24 hours. Solution pH was then adjusted to pH 10 using 1M NaOH. Solvents were removed under reduced pressure. Residue was dissolved in EtOAc (100 mL) and extracted with diH_2O (100 mL) 3x, brine (100 mL) 3x, organic layer was collected and dried over Na_2SO_4. EtOAc was then removed under reduced pressure.

Hydrolysis procedure of Monoethyl fumarate amides:

Monoethyl fumarate amide (10 mmol, 1 eq) was dissolved in EtOH (100 mL) and brought to 0˚C. 1 M NaOH (10 mmols, 1eq) was added dropwise via syringe. The solution was allowed to stir for 45 minutes at 0˚C, then moved to room temperature for 90 minutes. EtOH was removed under reduced pressure. Residue was dissolved in diH_2O (100 mL) and acidified to pH 2 using 1 M HCl. Solution was extracted with ether (100 mL) three time, and aqueous layer was collected. DiH_2O was then removed under reduced pressure.

TFA/DCM deprotection procedure of Boc protecting group:

Boc-AA_1-AA_2-OMe (30 mmols, 1 eq) sequence was dissolved in DCM (15 mL) and brought to 0˚C. Solution was then treated with an equal volume of TFA (15 mL). The reaction was allowed to stir at 0˚C for 30 minutes, then moved to room temperature for 1 hr. TFA and DCM were then removed under reduced pressure.

Morpholine coupling procedure:

H-AA_1-AA_2-AA_3 -OMe (1.24 mmol, 1 eq) was dissolved in DMF(10 mL) and brought to 0˚C. The solution was treated with morpholinoacetic acid (1.612 mmols, 1.3 eq) followed by dropwise addition of DIPEA (2.48mmols, 2 eq). In a separate round bottom flask, PyBop (1.984 mmols, 1.6 eq) was dissolved in DMF(10 mL) and added to the reaction solution at 0˚C. The solution was allowed to stir at 0˚C and left to reach room temperature overnight. DMF was removed under reduced pressure and residue dissolved in EtOAc(10 mL) and extracted with diH_2O (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL), the organic layer was collected and dried over Na_2SO_4. Crude was then triturated using diethyl ether, and subsequently purified by silica gel chromatography (10% MeOH/DCM).

Aza-peptide Michael acceptor inhibitor synthesis coupling procedure:

A solution of Pg-AA_1-AA_2-AA_3-$NHNHCH_2CH(CH_3)_2$ (0.314 mmols, 1eq) in dry DMF (20 mL) at 0˚C was treated with HOBt (1.25 mmols, 4 eq) and $R_{(2)}$-amide fumaric acid (1.25 mmols, 4eq) and allowed to stir for 15 min. The solution was then treated with EDC (1.25 mmols, 4 eq) and left to stir for 5 min at 0°C. Reaction was then stirred for 16 hours at room temperature. DMF was removed under reduced pressure and crude was dissolved in EtOAc (10 mL) and extracted 3x with saturated $NaHCO_3$ (10 mL) and brine (10 mL) then dried over Na_2SO_4. Crude was purified by silica gel chromatography (5% MeOH/DCM).

Solid phase peptide synthesis procedure:

Fmoc-Leu-Wang resin (0.160 mmols, 1 eq) was tested to be yellow using a Kaiser test and added to a separatory solid phase synthesis funnel. The beads were then swelled in DCM (10 mL), and rinsed 2x with DMF (10 mL). To the funnel, 20% piperdine in DMF (7 mL) was added and the mixture rotated for 15 min. The resin was then rinsed with DMF and another volume of 20%

piperdine in DMF (7 mL) was added to the funnel to rotate for an additional 5 min. The piperidine solution was then washed off and the resin was thoroughly rinsed 3x with DMF (10 mL), DCM (10 mL), DMF (10 mL), and the Kaiser test appeared blue indicating free amine. Next, a solution of HOBt (0.64 mmols, 4 eq), HBTU (0.64 mmols, 4 eq) , and Peptide sequence-OH (0.64 mmols, 4 eq) in DMF (10 mL)was added to the funnel, DIPEA (0.64 mmols, 4 eq)was then added dropwise, and the reaction was rotated for 30 min. The resin was then filtered and rinsed with DMF (10 mL). The reaction was repeated once on the same scale and under the same conditions. A Kaiser test was performed and appeared colorless indicating coupling is complete. To the funnel, 20% piperdine in DMF (7 mL) was added and the mixture rotated for 15 min. The piperdine solution was drained, beads were washed with DMF (10 mL) and a second volume 20% piperdine in DMF (7 mL) was added and the mixture was rotated for 5 min. A blue Kaiser test indicated free amine. Following, a solution of HOBt (0.64 mmols, 4 eq) , HBTU (0.64 mmols, 4 eq) , and Fmoc-peptide sequence-OH (0.64 mmols, 4 eq) in dry DMF was added to the funnel, with DIPEA (0.64 mmols, 4 eq) added dropwise. The reaction was rotated for 30 min. The reaction was repeated once on the same scale and under the same conditions. The solution was then drained, and beads were rinsed 3x with DMF (10 mL), DCM (10 mL), DMF (10 mL). A Kaiser test was performed and appeared clear. The solution was thoroughly washed with DCM (30 mL) and a solution of 1:1 DCM/TFA (10 mL) was added to the funnel and rotated for 1 hr. Following, the solution was drained from the beads. The beads were exhaustively rinsed with additional DCM (30 mL) to ensure complete collection of cleaved products. The organic solution was concentrated in vacuum.

Aza-Gln Side Chain Synthesis (step 1):

To a 50 mL round bottom, tert-Butyl-3-bromopropionate (3.932 mol, 1 eq) and tetrabutylammonium iodide (3.932 mmol, 1 eq) were added and allowed to pre-stir for 45 min at 55˚C in DMF (10 mL). Following, a solution of 9-Fluorenylmethyl Carbazate (3.932 mmol, 1 eq) in DMF (10 mL) was added and the solution was allowed to stir at 55˚C for 48 hr. DMF was removed using nitrogen gas. Residue was dissolved in EtOAc (10 mL) and extracted with diH_2O (10 mL), organic layer was collected and dried over Na_2SO_4. EtOAc was then removed under reduced pressure. Crude was then recrystallized using DCM. Collected solid was starting material, DCM was then removed under reduced pressure. Crude was titrated using diethyl ether and remaining crude was purified using column chromatography in 5% MeOH/DCM. Collected spots were again purified using column chromatography in 2:3 EtOAc: hexanes.

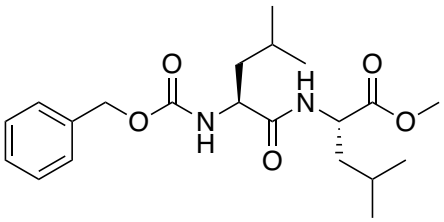
Epoxide Warhead Synthesis Step 1 (bromination):

Diethyl L-(+)-tartrate (48.5 mmol, 1 eq) was dissolved in of 33% HBr/AcOHneat (35 mL). The reaction was backfilled with N_2 and allowed to stir overnight at RT. Excess 33% HBr/AcOH was removed under reduced pressure.

Epoxide warhead synthesis Step 2 (acetoxy to hydroxy group):

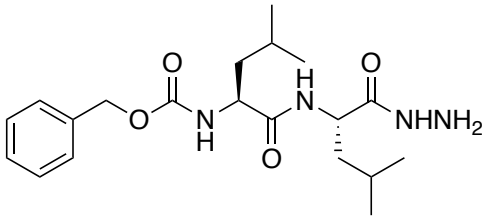
Diethyl 2-acetoxy-3-bromosuccinate (42.3 mmol, 1 eq) was treated with 33% HBr/AcOH (32 mL) in EtOH (200 mL) under reflux for 5 h. Following, and excess HBr/AcOH and solvent were removed in vacuo. Residue was purified via column chromatography (1:4 EtOAc/ Hexanes).

Synthesized Compounds



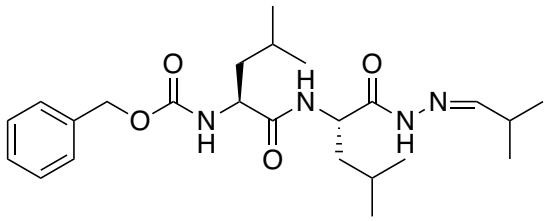
I

RA-1-1 (Methyl ((benzyloxy)carbonyl)-*L*-leucyl-*L*-leucinate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white solid (6.26 g, 16 mmol, 80% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.88 (m, Leu CH_3, 12H), 1.14-1.62 (m, Leu CH_2+CH, 6H), 3.60 (s, OMe, 3H), 4.05 (m, CH, 1H), 4.28 (t, CH, 1H), 5.02 (s, Cbz CH_2, 2H), 7.35 (m, Phenyl +NH, 6H), 8.24 (d, NH, 1H). HRMS (ESI) calcd for $[C_{21}H_{32}N_2O_5+Na]^+$ 415.2311, found 415.2746 (M+23), and 807.5566 (2M+23).



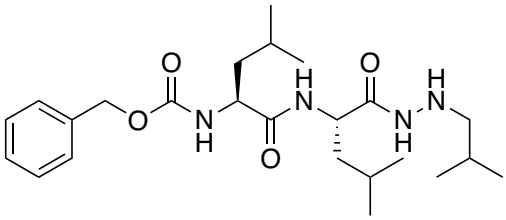
II

RA-1-3 (Benzyl ((*S*)-1-(((*S*)-1-hydrazineyl-4-methyl-1-oxopentan-2-yl) amino)-4-methyl-1-oxopentan-2-yl) carbamate). Refer to formation of hydrazide procedure for method and work up. Product produced as a white solid. (10.89 g, quantitative yield) ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.87 (m, Leu CH_3, 12H), 1.42 (m, Leu CH_2+CH, 6H), 4.07 (m, NH_2, 2H), 4.30 (m, 2CH, 2H), 5.06 (s, Cbz CH_2, 2H), 7.37 (m, Phenyl +NH, 6H), 7.86 (d, NH, 1H), 8.53 (d, NH, 1H). HRMS (ESI) calcd for $[C_{20}H_{32}N_4O_4+H]^+$ 393.2432, found 393.2891 (M+1), and 785.5695 (2M+23).



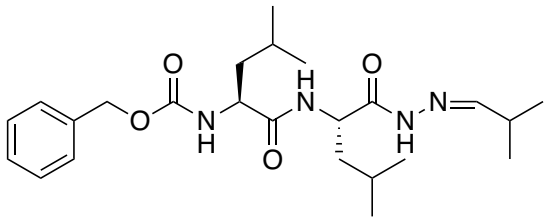
III

RA-1-5 (Benzyl ((*S*)-4-methyl-1-(((*S*)-4-methyl-1-(2-((*Z*)-2-methylpropylidene) hydrazineyl)-1-oxopentan-2-yl) amino)-1-oxopentan-2-yl) carbamate). Reductive Amination Procedure – Step 1 for method and work up. Product produced as a white solid (6.85 g, 15.5 mmol, 95% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.86-1.03 (m, Leu CH_3, 18H), 1.43-1.76(t, Leu CH_2+CH, 7H), 4.06 (m, C(alpha), 1H), 4.28 (m, C (alpha, 1H), 5.02 (m, Cbz CH_2, 2H), 7.37 (m, Phenyl +2NH, 8H), 7.78-7.97(d, =CH-, 1H), 10.87-11.11(s, NH, 1H). HRMS (ESI) calcd for $[C_{24}H_{38}N_4O_4+Na]^+$ 469.2893, found 469.3223 (M+23), and 915.76508 (2M+23).



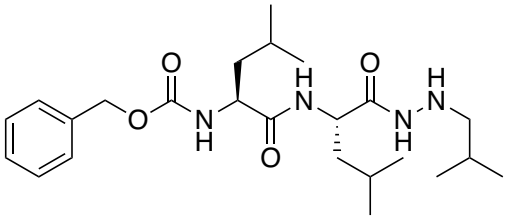
IV

RA-1-6 (Benzyl ((*S*)-1-(((*S*)-1-(2-isobutylhydrazineyl)-4-methyl-1-oxopentan-2-yl) amino)-4-methyl-1-oxopentan-2-yl) carbamate). Refer to reductive Amination Procedure – Step 2 ($NaCNBH_3$ Reduction) for method and work up. Product produced as a white solid (4.8 g, 10.7 mmol, 70 % yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.88-1.05 (m, Leu CH_3, 18H), 1.43-1.62(m, Leu CH_2+CH, 7H), 4.05 (m, C (alpha), 1H), 4.83(m, NH,1H), 5.03 (s, Cbz CH_2, 2H), 7.35 (m, Phenyl +NH, 6H), 7.84 (s, NH, 1H), 9.36 (s, NH, 1H). HRMS (ESI) calcd for $[C_{24}H_{40}N_4O_4+H]^+$ 449.3058, found 449.3544 (M+1), and 895.6860 (2M+1).



V

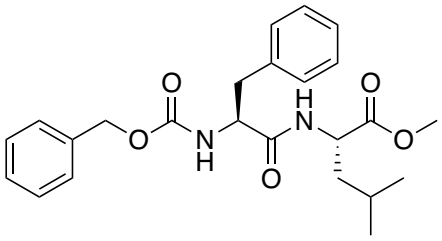
RA-1-7 (Benzyl ((*S*)-4-methyl-1-(((*S*)-4-methyl-1-(2-((*Z*)-2-methylpropylidene) hydrazineyl)-1-oxopentan-2-yl) amino)-1-oxopentan-2-yl) carbamate). Refer to Reductive Amination Procedure – Step 1 for method and work up. Product produced as a white solid (0.97 g, 2.17 mmol, 68% yield)**.** ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.86-1.05 (m, Leu CH_3, 18H), 1.44-1.76(m, Leu CH_2+CH, 7H), 4.06 (m, C (alpha), 1H), 4.28 (m, C (alpha, 1H), 5.03 (s, Cbz CH_2, 2H), 7.35 (m, Phenyl +1NH, 6H), 7.77(d, =CH-, 1H), 7.94 (d, NH,1H), 10.85-11.03(s, NH, 1H). HRMS (ESI) calcd for $[C_{24}H_{38}N_4O_4+H]^+$ 447.2901, found 447.3417 (M+1), and 915.6577 (2M+23).



VI

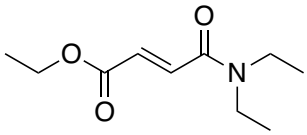
RA-1-8 (Benzyl ((*S*)-1-(((*S*)-1-(2-isobutylhydrazineyl)-4-methyl-1-oxopentan-2-yl) amino)-4-methyl-1-oxopentan-2-yl) carbamate). Refer to reductive Amination Procedure – Step 2 ($NaCNBH_3$ Reduction) for method and work up. Product produced as a white solid (2.212 g, quantitative yield)**.** ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.87-1.04 (m, Leu CH_3, 18H), 1.44-1.64 (m, Leu CH_2+CH, 7H), 4.05 (m, C (alpha), 1H), 4.26 (m, C (alpha, 1H), 4.82 (s, NH,1H), 5.03

(s, Cbz CH_2, 2H), 7.35 (m, Phenyl +NH, 6H), 7.84 (d, NH, 1H), 9.39 (s, NH, 1H). HRMS (ESI) calcd for $[C_{24}H_{40}N_4O_4+H]^+$ 449.3059, found 449.3554 (M+1).



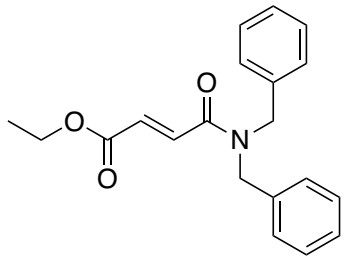
VII

RA-1-12 (methyl ((benzyloxy)carbonyl)-*L*-phenylalanyl-*L*-leucinate) Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white solid. (4.47 g, 10.48 mmol, 52% yield) ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.86-0.92 (m, Leu CH_3, 6H), 1.59-1.84 (m, Leu CH+ Leu CH_2, 3H), 2.74 (t, Phe CH_2, 1H), 3.00 (d, Phe CH_3, 1H), 3.62 (s, OMe, 3H), 4.32 (q, C (alpha), 2H), 4.94 (s, CH_2 (Cbz), 2H), 7.30 (m, Phenyl groups, 10H), 7.47 (d, NH, 1H), 8.38 (d, NH, 1H). HRMS (ESI) calcd for $[C_{24}H_{30}N_2O_5+Na]^+$ 449.2155, found 449.2852 (M+23), and 875.5816 (2M+23).



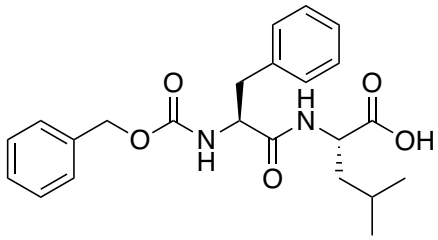
VIII

RA-1-13 (ethyl (*E*)-4-(diethylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a pink oil. (2.38 g, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 1.06-1.12 (m, amine CH_3, 6H), 1.24 (m, CH_3, 3H), 3.24 (m, $2CH_2$, 4H), 4.18 (q, CH_2-O, 2H), 6.58 (d, H, 1H), 7.35 (d, H,1H). HRMS (ESI) calcd for $[C_{24}H_{40}N_4O_4+H]^+$ 200.1208, found 200.1515 (M+1), 421.2757 (2M+23).



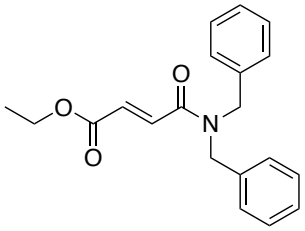
IX

RA-1-14 (ethyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate) Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a yellow oil. (5.3756 g, 16.63 mmols, 83.2% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 1.23 (m, CH_3 , 3H), 4.16 (q, CH_2 , 2H), 4.69 (d, CH_2, 2H), 6.74 (d, H, 1H), 7.20 (d, H, 1H), 7.44 (m, phenyl group, 10H). HRMS (ESI) calcd for $[C_{20}H_{21}NO_3+Na]^+$ 346.1521, found 346.1764 (M+23), 669.3618 (2M+23).



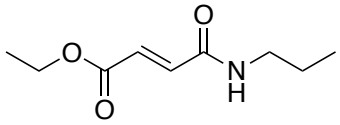
X

RA-1-15 (((benzyloxy)carbonyl)-*L*-phenylalanyl-*L*-leucine). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a white solid. (3.04 g, 7.38 mmols, 97.0% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.86-0.91 (m, Leu CH_3, 6H), 1.55-1.65 (m, Leu CH+ Leu CH_2, 3H), 2.75 (t, Phe CH_2, 1H), 3.01 (d, Phe CH_3, 1H), 4.04 (q, 2C (alpha), 2H), 4.94 (s, CH_2 (Cbz), 2H), 7.31 (m, Phenyl groups, 10H), 7.46 (d, NH, 1H), 8.22 (d, NH, 1H), 12.54 (s, OH, 1H). HRMS (ESI) calcd for $[C_{23}H_{28}N_2O_5+Na]^+$ 435.1998, 435.2297(M+23), 847.4676 (2M+23).



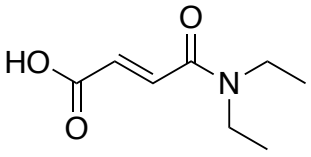
XI

RA-1-18 (ethyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate) Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a Yellow Oil. (3.96 g, 12.25 mmols, 61% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 1.21 (m, CH_3, 3H), 4.03- 4.17 (m. CH_2, 2H), 4.61- 4.68 (d, dibenzyl CH_2, 4H), 6.67-6.70 (d, tran H, 1H), 7.19-7.28 (m, Phenyl, 10H), 7.42 (d, trans H, 1H). HRMS (ESI) calcd for $[C_{20}H_{21}NO_3+H]^+$ 324.1521, found 324.1955 (M+1), and 647.3832 (2M+1).



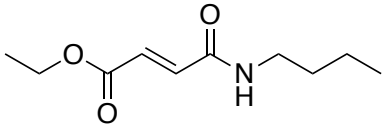
XII

RA-1-20 (ethyl (*E*)-4-oxo-4-(propylamino)but-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a yellow solid. (3.0981g, 16.72 mmols, 83.6% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 8.49 (s, NH, 1 H), 7.01 (d, H trans, 1 H), 6.55 (d, H trans, 1 H), 4.17 (q, CH_2, 2 H), 3.11 (q, CH_2, 2 H), 1.59 (m, CH_2, 2H), 1.25 (m, CH_3, 3 H), 0.86 (M, CH_3, 3 H). HRMS (ESI) calcd for $[C_9H_{17}NO_3+Na]^+$ 208.1052, found 208.1184 (M+23), and 393.2422 (2M+23).



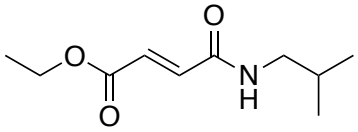
XIII

RA-1-21 ((*E*)-4-(diethylamino)-4-oxobut-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a Clear Oil. (48mg, 0.282 mmols, 12.0% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 1.06-1.41 (m, CH_3, 6H), 3.35 (m, CH_2, 4H), 6.54 (d, trans H, 1H), 7.25 (d, trans H, 1H), 12.87 (s, OH, 1H). HRMS (ESI) calcd for $[C_8H_{13}NO_3+Na]^+$ 194.0895, found 194.0920 (M+23), and 365.1947 (2M+23).



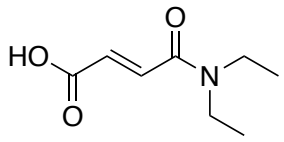
XIV

RA-1-22 (ethyl (*E*)-4-(butylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a yellow solid. (2.5231 g, 12.6 mmols, 63.0% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.86 (m, CH_3, 3H), 1.16-1.24 (m, CH_2+CH_3, 5H), 1.41 (m, CH_2, 2H), 2.95 (m, CH_2, 2H), 4.17 (m, CH_2, 2H), 6.54 (d, trans H, 1H), 6.99 (d, trans H, 1H), 8.47 (s, NH, 1H). HRMS (ESI) calcd for $[C_{10}H_{17}NO_3+Na]^+$ 222.1208, found 222.1367 (M+23), and 421.2792 (2M+23).



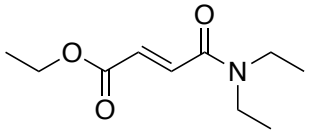
XV

RA-1-23 (ethyl (*E*)-4-(isobutylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a yellow solid. (2.74 g, 13.8mmols, 69.0% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.86 (m, $2CH_2$, 6H), 1.25 (m, CH_3, 3H), 1.72 (m, CH, 1H), 3.00 (m, CH_2, 2H), 4,19 (q, CH_2, 2H), 6.56 (d, trans H, 1H), 7.04 (d, trans H, 1H), 8.49 (s, NH, 1H). HRMS (ESI) calcd for $[C_{10}H_{17}NO_3+H]^+$ 200.1208, found 200.1530 (M+1).



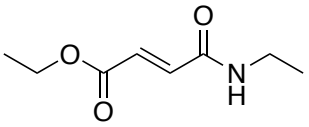
XVI

RA-1-24 ((*E*)-4-(diethylamino)-4-oxobut-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a pink solid. (2.07 g, 12.20 mmols, 91% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 1.04-1.11 (m, 2 CH_3 , 6 H), 3.33 (m, 2CH_2 + H_2O, 6H), 6.51 (d, H trans, 1 H), 6.75 (d, H trans, 1 H). HRMS (ESI) calcd for $[C_8H_{13}NO_3+Na]^+$ 194.0895, found 194.1122 (M+23).



XVII

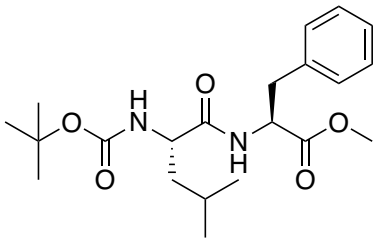
RA-1-25 (ethyl (*E*)-4-(diethylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF coupling procedure for method and work up. Product produced as a red oil. (2.6486 g, 13.40 mmols, 67%). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.90- 1.06 (m, 2CH_3, 6 H), 1.12- 1.24 (m, CH_3, 3 H), 3.19- 3.30 (m, 2 N-CH_2, 4 H), 4.19 (m, O-CH_2, 2H), 6.57 (d, H trans, 1 H), 7.35 (d, H trans, 1H). HRMS (ESI) calcd for $[C_{10}H_{17}NO_3+Na]^+$ 222.0895, found 222.1237 (M+23), and 421.2589 (2M+23).



XVIII

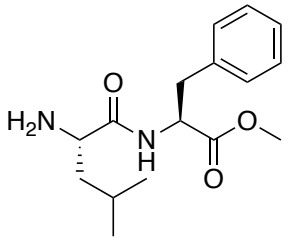
RA-1-28 (ethyl (*E*)-4-(ethylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a yellow solid. (1.266 g, 7.40

mmols, 37% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.88- 1.06 (m, CH_3, 3 H), 1.24 (m, CH_3, 3 H), 3.18 (m, N-CH_2, 2 H), 4.18 (m, O-CH_2, 2 H), 6.57 (d, H trans, 1 H), 6.96 (d, H trans, 1 H), 8.52 (s, NH, 1 H). HRMS (ESI) calcd for $[C_8H_{13}NO_3+Na]^+$ 194.0895, found 194.1014 (M+23), and 365.2085 (2M+23).



XIX

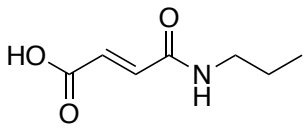
RA-1-29 (methyl (*tert*-butoxycarbonyl)leucylphenylalaninate). Refer to general NMM and iBCF coupling procedure for method and work up. Product produced as a white solid. (12.24 g, 31.2 mmols, 78% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.84 (m, 2 CH_3, 6 H). 1.18- 1.52 (m, 2 CH_3 + CH_2 + alpha C, 12H), 2.95 – 3.01 (m, CH_2, 2 H), 3.58 (s, CH_3, 3 H), 3.96 (q, alpha C, 1H), 4.49 (q, alpha C, 1 H), 6.80 (d, NH, 1 H), 7.22- 7.25 (m, phenyl, 5 H), 8.13 (d, NH, 1H). HRMS (ESI) calcd for $[C_{21}H_{32}N_2O_5+Na]^+$ 415.2311, found 415.2482 (M+23), and 807.5110 (2M+23).



XX

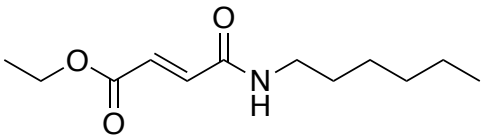
RA-1-30 (methyl leucylphenylalaninate). Refer to TFA/DCM deprotection of Boc protecting group procedure for method and work up. Product produced as a Clear oil. (9.12 g, 31.2 mmols, Quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.89 (t, 2 CH_3, 6H), 1.54 (t, CH_2, 2 H),

1.65 (q, apla C, 1 H), 3.00-3.06 (m, CH_2, 2 H), 3.60 (s, CH_3, 3 H), 3.77 (m, alpha C, 1 H), 4.56 (q, alpha C, 1 H), 7.27 (m, phenyl, 5 H), 8.12 (s, NH, 1 H), 8.98 (d, NH, 1 H). HRMS (ESI) calcd for $[C_{16}H_{24}N_2O_3+Na]^+$ 293.1787, found 293.2200 (M+1), and 585.4321 (2M+1).



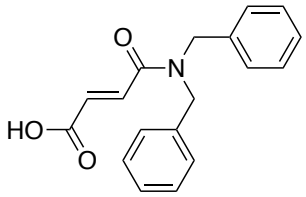
XXI

RA-1-31 ((*E*)-4-oxo-4-(propylamino)but-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a yellow solid. (0.430 g, 2.74 mmols, 99% yield). ^{1}H NMR (MeOD-*d*$_4$, 400MHz) δ: 0.9408 (m, CH_3, 3 H), 1.5496-1.5684 (q, CH_2, 2 H), 3.2114 (t, CH_2, 2 H), 6.6364 (d, H trans, 1 H), 6.7666 (d, H trans, 1 H). HRMS (ESI) calcd for $[C_7H_{11}NO_3+Na]^+$ 180.0739, found 180.0850 (M+23), and 337.1744 (2M+23).



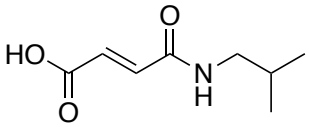
XXII

RA-1-32 (ethyl (*E*)-4-(hexylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white solid. (3.50 g, 15.4 mmols, 77% yield). ^{1}H NMR (DMSO-*d*$_6$, 400MHz) δ: 0.8611 (m, CH_3, 3 H). 1.2327 (m, 4 CH_3, 9 H), 1.4273 (m, CH_2, 2 H), 3.1436 (q, CH_2, 2 H), 4.1758 (q, CH_2, 2 H), 6.5645 (d, H trans, 1 H), 6.9833 (d, H trans, 1 H), 8.4814 (s, NH, 1 H). HRMS (ESI) calcd for $[C_{10}H_{17}NO_3+Na]^+$ 250.1208, found 250.1708 (M+23), and 477.3481 (2M+23).



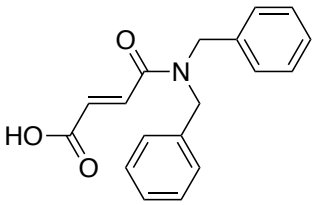
XXIII

RA-1-33 ((*E*)-4-(dibenzylamino)-4-oxobut-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a yellow solid. (0.56 g, 1.597 mmols, 98% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 4.5626 (m, 2 CH_2, 4 H), 6.6908 (d, H trans, 1 H), 6.8150 (d, H trans, 1 H), 7.2539- 7.3532 (m, phenyl, 10 H). HRMS (ESI) calcd for $[C_{18}H_{17}NO_3+Na]^+$ 318.1208, 318.1456 (M+23), and 613.2994 (2M+23).



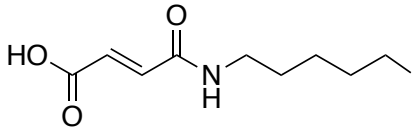
XXIV

RA-1-34 ((*E*)-4-(isobutylamino)-4-oxobut-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a yellow solid. (2.90 g, 11.22 mmols, 86% yield). ^{1}H NMR: Solvent: MeOD-d_4. 0.9194- 0.9361 (m, 2 CH_3, 6 H), 1.8152 (m, alpha C, 1 H), 3.0689- 3.0862 (d, CH_2, 2 H), 6.6213-6.6601 (d, trans H, 1 H), 6.7692- 6.8080 (d, trans H, 1 H). HRMS (ESI) calcd for $[C_8H_{13}NO_3+Na]^+$ 194.0895, found 194.1026 (M+23), and 365.2091 (2M+23).



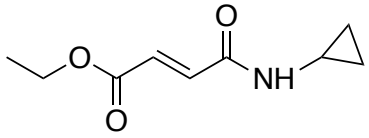
XXV

RA-1-35 ((*E*)-4-(dibenzylamino)-4-oxobut-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a yellow solid. (1.70 g, 5.77 mmols, 95% yield).^{1}H NMR (DMSO-d_6, 400MHz) δ: 4.5557 – 4.5874 (d, 2 CH_2, 4 H), 6.6870 (d, trans H, 1 H), 6.7900 (d, trans H, 1 H), 7.2496- 7.3605 (m, phenyl, 10 H). HRMS (ESI) calcd for $[C_{18}H_{17}NO_3+Na]^+$ 318.1208, found 318.1484 (M+23), and 613.3032 (2M+23).



XXVI

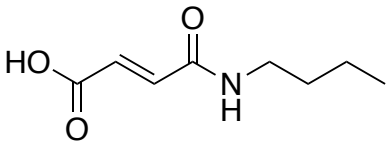
RA-1-36 ((*E*)-4-(hexylamino)-4-oxobut-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a yellow solid. (2.75 g, 13.85 mmols, 95% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8654 (m, CH_3, 3 H), 1.2539 (m, 3 CH_2, 6 H), 1.4011 (m, CH_2, 2 H), 3.0848- 3.1672 (q, CH_2, 2 H), 6.3639 (d, trans H, 1 H), 6.4640 (d, trans H, 1 H), 8.0182 (t, NH, 1 H). HRMS (ESI) calcd for $[C_8H_{13}NO_3+Na]^+$ 222.1208, found 222.1386 (M+23), and 421.2811 (2M+23).



XXVII

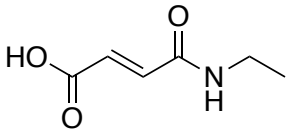
RA-1-38 (ethyl (*E*)-4-(cyclopropylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white solid. (0.8422 g, 4.6 mmols, 23% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.4570 (m, CH_2, 2 H), 0.6944 (m, CH_2, 2 H), 1.2404 (m, CH_3, 3 H), 2.7598 (m, alpha C, 1 H), 4.1723 (q, CH_2, 2 H), 6.5463 (d,

trans H, 1 H), 6.9024 (d, trans H, 1 H), 8.5642 (s, NH, 1 H). HRMS (ESI) calcd for $[C_9H_{13}NO_3+Na]^+$ 206.0895, found 206.1054 (M+23), and 389.2139 (2M+23).



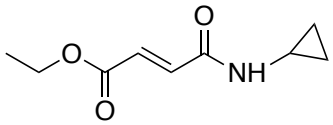
XXVIII

RA-1-39 ((*E*)-4-(butylamino)-4-oxobut-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a yellow solid. (2.096 g, 12.26 mmols, quantitative yield). ^{1}H NMR (MeOD-d_4, 400MHz) δ: 0.9460 (m, CH_3, 3 H), 1.3786 (m, CH_2, 2 H), 1.5307 (m, CH_2, 2 H), 3.2564 (m, CH_2, 2 H), 6.6125 (d, trans H, 1 H), 6.7789 (d, trans H, 1 H). HRMS (ESI) calcd for $[C_8H_{13}NO_3+Na]^+$ 194.0895, found 194.1050 (M+23), and 365.2120 (2M+23).



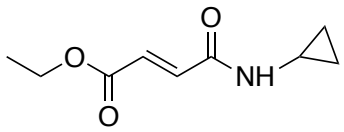
XXIX

RA-1-40 ((*E*)-4-(ethylamino)-4-oxobut-2-enoic acid). Refer to hydrolysis of monoethyl fumarate amides procedure for method and work up. Product produced as a yellow solid. (1.1819 g, 7.36 mmols, quantitative yield). ^{1}H NMR (MeOD-d_4, 400MHz) δ: 1.1789 (m, CH_3, 3 H), 3.2896- 3.3324 (m, CH_2, 2 H), 6.6316 (d, trans H, 1 H), 6.8027 (d, trans H, 1 H). HRMS (ESI) calcd for $[C_6H_9NO_3+Na]^+$ 166.0582, found 166.0706 (M+23).



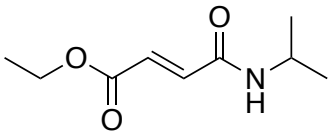
XXX

RA-1-41 (ethyl (*E*)-4-(cyclopropylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white solid. (4.83 g, 26.4 mmols, 66% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.4597 (m, CH_2, 2 H) , 0.5542-0.6896 (m, CH_2, 2 H), 1.2378 (m, CH_3, 3 H), 2.7585 (q, alpha C, 1 H), 4.1731 (q, CH_2, 2 H), 6.5484 (d, trans H, 1 H), 6.8962 (d, trans H, 1 H), 8.5643 (s, NH, 1 H). HRMS (ESI) calcd for $[C_9H_{13}NO_3+Na]^+$ 206.0895, found 206.0921 (M+23), and 389.1934 (2M+23).



XXXI

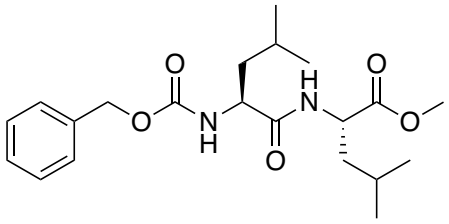
RA-1-44 (ethyl (*E*)-4-(cyclopropylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white solid. (0.183 g, 13.6 mmols, 34% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.4574 (m, CH_2, 2 H) , 0.6879 (m, CH_2, 2 H), 1.2336 (m, CH_3, 3 H), 2.7588 (q, alpha C, 1 H), 4.1748 (q, CH_2, 2 H), 6.5678 (d, trans H, 1 H), 6.9227 (d, trans H, 1 H), 8.5656 (s, NH, 1 H). HRMS (ESI) calcd for $[C_9H_{13}NO_3+Na]^+$ 206.0895, found 206.1022 (M+23), and 389.2091 (2M+23).



XXXII

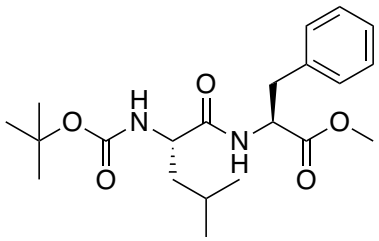
RA-1-45 (ethyl (*E*)-4-(isopropylamino)-4-oxobut-2-enoate). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a yellow solid. (2.14 g, 11.6 mmols, 58% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: d_6.1.0862 (m, 2 CH_3, 6 H), 1.2310 (m, CH_3, 3 H), 3.918 (q, CH, 1 H), 4.1861 (q, CH_2, 2 H), 6.5752 (d, trans H, 1 H), 6.9628 (d, trans H,

1 H), 8.4005 (s, NH, 1 H). HRMS (ESI) calcd for $[C_9H_{15}NO_3+Na]^+$ 208.0895, found 208.1362 (M+23), and 393.2761 (2M+23).



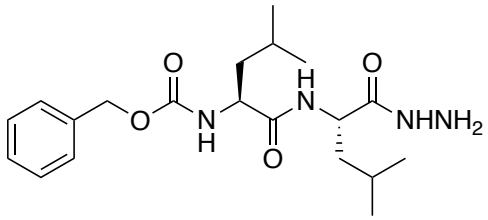
XXXIII

RA-1-47. Methyl ((benzyloxy)carbonyl)- *L*-leucyl-*L*-leucinate. (20 mmols). Product produced as a white solid. (6.60 g, 16.8mmols, 84 % yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.88 (m, 4-Leu's CH_3, 12H), 1.42-1.64 (m, CH_2+CH+CH),3.61 (s, CH_3, 3H), 4.08 (q, CH, 1H), 4.26 (q, CH, 1H), 5.01 (s, CH_2,2H), 7.35 (m, phenyl+ NH, 6H), 8.21 (d, NH, 1H). HRMS (ESI) calcd for $[C_{21}H_{32}N_2O_5+Na]^+$ 415.2311, found 415.2660 (M+23) and 807.5390 (2M+23).



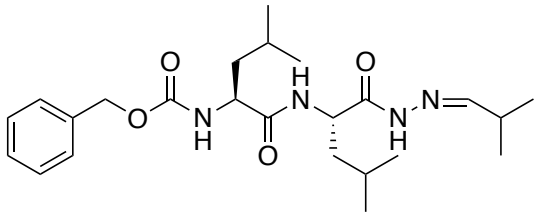
XXXIV

RA-1-48. Methyl (*tert*-butoxycarbonyl)-*L*-leucyl-*L*-phenylalaninate. Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as white solid. (14.10 g, 35.92 mmols, 89% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.82-0.87 (m, Leu CH_3, 6H), 1.28-1.37 (m, Leu CH_2+ boc, 11H), 1.52 (m, Leu CH, 1H), 2.97-3.01 (m, phe CH_2, m), 3.57(s, CH_3, 3H), 3.96 (q, CH, 1H), 4.49 (q, CH, 1H), 6.80 (d, NH, 1H), 7.21-7.25 (m, phenyl, 5H), 8.21 (d, NH, 1H). HRMS (ESI) calcd for $[C_{21}H_{32}N_2O_5+Na]^+$ 415.2311, found 415.2674 (M+23) and 807.5408 (2M+23).



XXXV

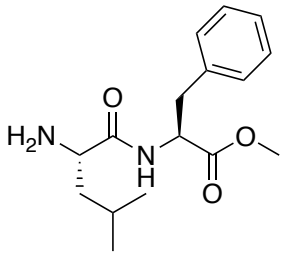
RA-1-49. Benzyl ((*S*)-1-(((*S*)-1-hydrazineyl-4-methyl-1-oxopentan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate. Refer to formation of hydrazide procedure for method and work up. Product produced as a white solid. (6.92 g, 16.83 mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.86 (m, Leus CH_3, 12H), 1.47-1.59 (m, Leus CH_2 +CH, 6H), 4.05 (q, CH, 1H), 4.20 (s, NH, 2H), 4.28 (q, CH, 1H), 5.03 (s, CH_2, 2H), 7.35-7.41 (m, Phenyl+NH, 6H), 7.80 (d, NH, 1H), 9.13 (s, NH, 1H). HRMS (ESI) calcd for $[C_{20}H_{32}N_4O_4+Na]^+$ 415.2424, found 415.2805 (M+23) and 807.5677 (2M+23).



XXXVI

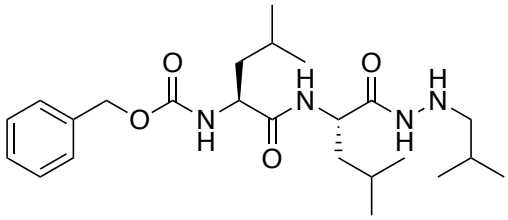
RA-1-50. **Benzyl ((*S*)-4-methyl-1-(((*S*)-4-methyl-1-(2-((*Z*)-2-methylpropylidene)hydrazineyl)-1-oxopentan-2-yl)amino)-1-oxopentan-2-yl)carbamate.** Refer to Reductive Amination Procedure – Step 1 for method and work up. Product produced as a white solid. (7.90 g, 17.65 mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8818 (m, $4CH_3$, 12H), 1.0419 (m, $2CH_2$, 6H), 1.4329-1.6411 (m, 2CH+ $2CH_2$, 6H), 2.4616 (m, CH, 1H), 4.0659 (m, CH, 1H), 4.2986 (q, CH, 1H), 5.0334 (s, CH_2, 2H), 7.6480 (m, phenyl+

NH, 6H), 7.7889- 7.9481 (d, NH, 1H), 10.8506-11.0220 (s, NH, 1H). HRMS (ESI) calcd for $[C_{24}H_{82}N_4O_4+Na]^+$ 446.2893, found 469.3366 (M+23) and 915.6783 (2M+23).



XXXVII

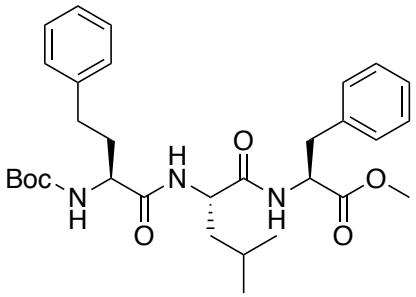
RA-1-51. Methyl *L*-leucyl-*L*-phenylalaninate. Refer to TFA/DCM deprotection of Boc protecting group procedure for method and work up. Product produced as a clear oil. (20.95 g, 35.92 mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.9036 (t, 2CH_3, 6H), 1.5323-1.6632 (m, CH+CH_2, 3H), 2.9990-3.0645 (m, CH_2, 2H), 3.6015 (s, CH_3, 3H), 3.7979 (m, CH, 1H), 4.5575 (m, CH, 1H), 7.2553 (m, phenyl, 5H), 8.1721 (s, 3NH, 3H), 8.9840 (d, NH, 1H). HRMS (ESI) calcd for $[C_{16}H_{24}N_2O_3+H]^+$ 293.1787, found 293.2229 (M+1), and 585.4366 (2M+23).



XXXVIII

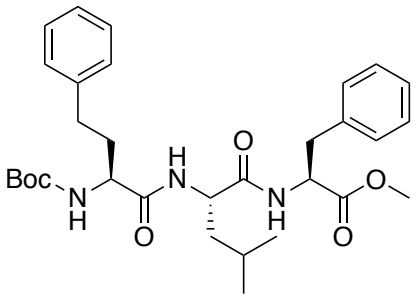
RA-1-52. Benzyl ((*S*)-1-(((*S*)-1-(2-isobutylhydrazineyl)-4-methyl-1-oxopentan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate. Refer to reductive Amination Procedure – Step 2 ($NaCNBH_3$ Reduction) for method and work up. Residue was then recrystallized using 1:1 hexanes and ethyl acetate. Product produced as a white solid. (1.6732 g, 17.60 mmols, 22% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8350 (m, 6CH_3, 18H), 1.4158-1.6193 (m, CH+CH_2,

7H), 2.4442 (t, CH2, 2H), 4.0431 (q, CH, 1H), 4.2570 (q, CH, 1H), 4.8171 (t, CH, 1H), 5.0309 (s, CH_2, 2H), 7.3733 (m, phenyl+ NH, 6H), 7.8316 (d, NH, 1H), 9.3592 (d, NH, 1H). HRMS (ESI) calcd for $[C_{24}H_{40}N_4O_4+H]^+$ 449.3050, found 449.3543 (M+1), and 919.6847 (2M+23).



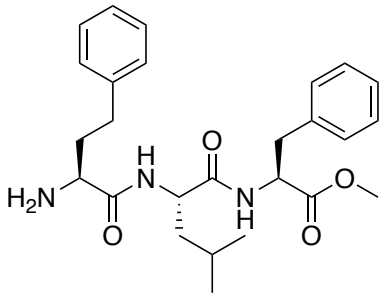
XXXIX

RA-1-54. Methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a White solid. (6.66 g, 17.30 mmols, 71% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8513-0.9036 (m, $2CH_3$, 6H), 1.4013-1.5585 (m, boc+ CH+ CH_2, 11H), 1.8597 (m, Hphe CH_2, 2H), 2.6323 (m, Hphe CH_2, 2H), 2.9990 (m, phe CH_2, 2H), 3.5884 (s, CH_3, 3H), 3.9420 (m, CH, 1H), 4.4134-4.4920 (m, CH, 1H), 7.2029- 7.2553 (m, phenyl +NH, 11H), 8.6042 (d, NH, 1H), 95079 (d, NH, 1H). HRMS (ESI) calcd for $[C_{31}H_{43}N_3O_6+Na]^+$ 576.3152, found 576.4008 (M+23).



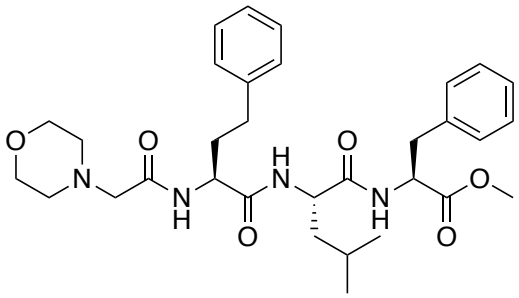
XL

RA-1-56. Methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to general NMM and iBCF Coupling procedure for method and work up. Crude was also titrated with hexanes. Product produced as a white solid. (1.53 g, 6.50 mmols, 42% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8685 (m, 2CH_3, 6H), 1.3998 (m, Boc+ CH_2, 11H), 1.6041 (m, Hphe CH_2, 2H), 2.5952 (m, Hphe CH_2, 2H), 2.9426-3.0141 (m, phe CH_2, 2H), 3.5249 (s, CH_3, 3H), 3.9132 (m, CH, 1H), 4.3627-4.4343 (m, 2CH, 2H), 7.1725- 7.2849 (m, Phenyl +NH, 11H), 7.7344 (d, NH, 1H), 8.3679 (d, NH, 1H). HRMS (ESI) calcd for $[C_{31}H_{43}N_3O_6+Na]^+$ 553.3152, found 576.3594 (M+23).



XLI

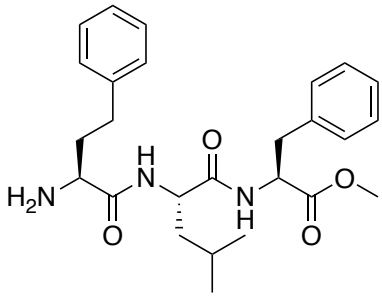
RA-1-57. Methyl ((*S*)-2-amino-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to TFA/DCM deprotection of Boc protecting group procedure for method and work up. Product produced as a white solid. (1.72 g, 2.00 mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.90 (m, Leu CH_3, 6H), 1.44 (t, Leu CH_2, 2H), 1.63 (q, CH, 1H), 1.92 (m, Hphe CH_2, 2H), 2.55 (m, Hphe CH_2, 2H), 2.95-3.03 (m, Phe CH_2, 2H), 3.55 (s, CH_3, 3H), 3.87 (m, CH, 1H), 4.44-4.49 (m, CH, 2H), 7.18 (m, phenyl, 10H), 8.18 (s, NH, 3H), 8.57 (m, NH, 2H). HRMS (ESI) calcd for $[C_{26}H_{35}N_3O_4+H]^+$ 454.2628, found 454.3565 (M+1).



XLII

RA-1-58. Methyl ((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to Morpholine coupling procedure for method and work up.

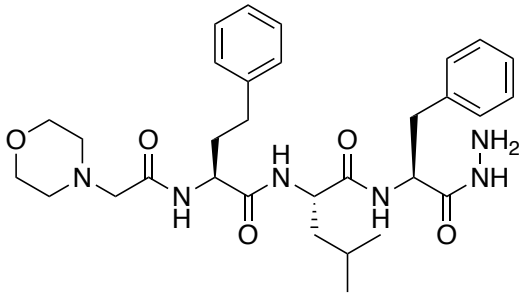
Product produced as a white solid. (0.3333 g, 1.240 mmols, 42% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.83-0.89 (dd, Leu CH_3, 6H), 1.41 (t, CH_2, 2H), 1.56 (q, CH, 1H), 1.73-1.84 (m, Hphe+ CH_2, 4H), 2.45 (s, CH_2+ Hphe CH_2, 4H), 2.97-3.01 (m, N-CH_2, 4H), 3.53-3.51 (s+t, O-CH_2+ CH_3, 7H), 4.37-4.45 (m, 3CH, 3H), 7.18-7.28 (m, phenyl, 2H), 7.89 (d, NH, 1H), 8.04 (d, NH, 1H), 8,37 (d, NH, 1H). HRMS (ESI) calcd for $[C_{32}H_{44}N_4O_6+H]^+$ 581.3261, found 581.4422 (M+1).



XLIII

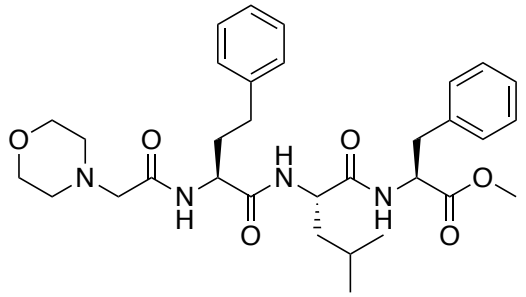
RA-1-59. Methyl ((*S*)-2-amino-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to TFA/DCM deprotection of Boc protecting group procedure for method and work up. Product produced as a white solid. (0.5074 g,0.77 mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: . 0.89-0.92 (m, Leu CH_3, 6H), 1.45 (m, CH_2, 2H), 1.63 (m, CH, 1H), 2.55 (m, Hphe

CH_2, 2H), 2.95-3.03 (m, Phe CH_2, 2H), 3.54 (s, CH_3, 3H), 3.88 (q, CH, 1H), 4.44-4.50 (m, 2CH, 2H), 7.07-7.31 (m, Phenyl, 10H), 0.82 (s, NH_2, 2H), 8.57 (m, NH, 2H). HRMS (ESI) calcd for $[C_{26}H_{35}N_3O_4+H]^+$ 454.2628, found 454.3543 (M+1).



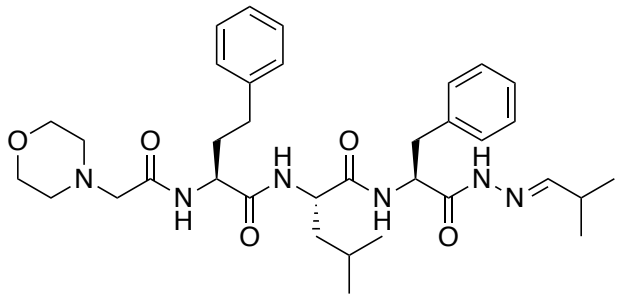
XLIV

RA-1-60. (*S*)-*N*-((*S*)-1-hydrazineyl-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide. Refer to formation of hydrazide procedure for method and work up. (0.0806 g, 0.178 mmols, 78% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8285-0.8718 (dd, leu-CH_3, 6H), 1.3905 (m, Leu CH_2, 2H), 1.5346 (q, Leu CH, 1H), 1.7436 (q, Hphe CH_2,2H), 1.8660 (m, CH_2, 2H), 2.4424 (s, CH_2+ Hphe CH_2, 4H), 2.8243-3.0260 (m, N-CH_2+ phe CH_2, 6H), 3.6168 (t, O-CH_2, 4H), 4.2004 (s, NH_2, 2H), 4.3517-4.4381 (m, 3CH, 3H), 7.0967- 7.2840 (m, phenyl +NH, 11H), 7.8892 (d, NH, 1H), 8.0261 (d, NH, 1H), 9.0996 (s, NH, 1H). HRMS (ESI) calcd for $[C_{31}H_{44}N_6O_5+H]^+$ 581.3373, found 581.4066 (M+1).



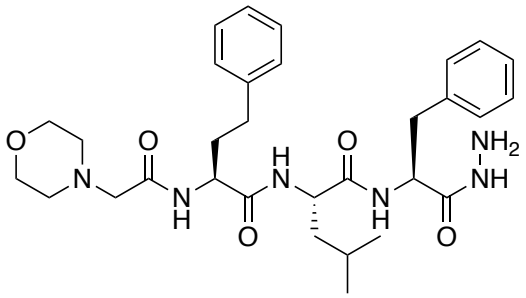
XLV

RA-1-61. Methyl ((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to Morpholine coupling procedure for method and work up. (0.264 g, 3.370 mmols, 14% yield). Product produced as a white solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.85-0.89 (dd, Leu CH_3, 6H), 1.24 (q, Leu CH_2, 2H), 1.57 (m, CH, 1H), 1.84 (q, Hphe CH_2, 2H), 2.88 (m, CH_2, 2H), 2.46 (s, CH_2+ Hphe CH_2, 4H), 2.96-3.03 (m, N-CH_2+phe CH_2, 6H), 3.55 (s, CH_3, 3H), 3.62 (t, O-CH_2, 4H), 4.38 (m, CH, 1H), 4.47 (q, CH, 1H), 7.19-7.28 (m, phenyl, 10H), 7.89 (s, NH, 1H), 8.07 (d, NH, 1H), 8.37 (d, NH, 1H). HRMS (ESI) calcd for [$C_{33}H_{46}N_4O_6$+H]$^+$ 581.3417, found 581.3790 (M+1).



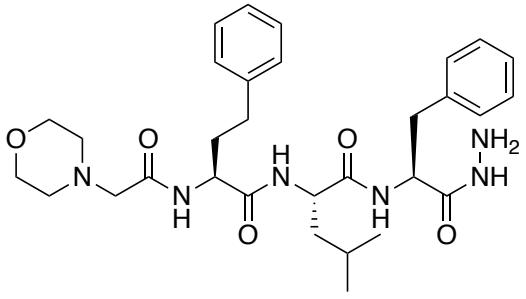
XLVI

RA-1-62. (*S*)-*N*-((*S*)-1-(isopropyldiazenyl)-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide. Refer to Reductive Amination Procedure – Step 1 for method and work up. (0.0626 g, 0.138 mmols, 72% yield). Product produced as a white solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8111-0.8608 (dd, Leu CH_3, 6H), 1.0200 (m, CH_3, 6H), 1.3887 (m, Leu CH_2, 2H), 1.5362 (q, leu CH, 1H), 1.8086-1.9172 (m, CH_2, 2H), 2.4456 (s+m, CH_2+ homophe CH_2, 4H), 2.8635-2.9618 (m, N-CH_2, 4H), 3.6009 (t, O-CH_2, 4H), 4.3628-4.4489 (m, 2CH, 2H), 5.4354 (q, CH, 1H), 7.1895- 7.3492 (m, Phenyl, 10H), 7.8777 (d, NH, 1H), 8.0129 (m, NH, 1H), 11.0000 (d, NH, 1H). HRMS (ESI) calcd for [$C_{35}H_{50}N_6O_5$+H]$^+$ 635.3843, 635.4423 (M+1).



XLVII

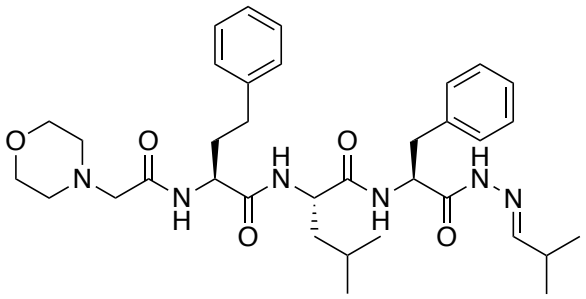
RA-1-63. (*S*)-*N*-((*S*)-1-hydrazineyl-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide. Refer to formation of hydrazide procedure for method and work up. (0.2027 g, 0.3485 mmols, 96% yield). Product produced as a white solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8108-0.8578 (dd, 2CH_3, 6H), 1.3984-1.5278 (m, CH+CH_2, 3H), 1.7391- 1.8567 (m, Hphe CH_2+ CH_2, 4H), 2.4442 (s, CH_2+ Hphe CH_2, 4H), 2.8202- 2.9730 (m, phe CH_2 + N-CH_2, 6H), 3.6193 (t, O-CH_3, 4H), 4.1833 (s, NH_2, 2H), 4.3479-4.4301 (m, 3CH, 3H), 7.1661-7.2621 (m, phenyl, 10H), 7.8849- 8.0377 (d, 3NH, 3H), 9.0952 (s, NH, 1H). HRMS (ESI) calcd for $[C_{31}H_{44}N_6O_5+H]^+$ 581.3373, found 581.3913 (M+1).



XLVIII

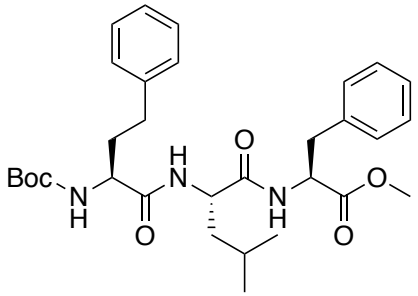
RA-1-64. (*S*)-*N*-((*S*)-1-hydrazineyl-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide. Refer to formation of hydrazide procedure for method and work up. Product produced as a white solid. (0.2528 g, 0.4368 mmols, 96% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8062-0.8675 (dd, Leu CH_3, 6H), 1.3982 (q,

CH_2, 2H), 1.5308 (q, CH, 1H), 1.8678 (m, CH_2, 2H), 2.4391 (s+m, CH_2 +phe CH_2, 4H), 2.8065-2.9698 (m, N-CH_2, 4H), 3.6026 (t, O-CH_2, 4H), 4.1537 (s, NH_2, 2H), 4.3272 (m, CH, 1H), 4.4496 (q, CH, 1H), 7.1643-7.2766 (m, phenyl, 10H), 7.8889 (d, NH, 1H), 8.0318 (d, NH, 1H), 9.0932 (s, NH, 1H). HRMS (ESI) calcd for $[C_{31}H_{44}N_6O_5+H]^+$ 581.3373, found 581.3902 (M+1).



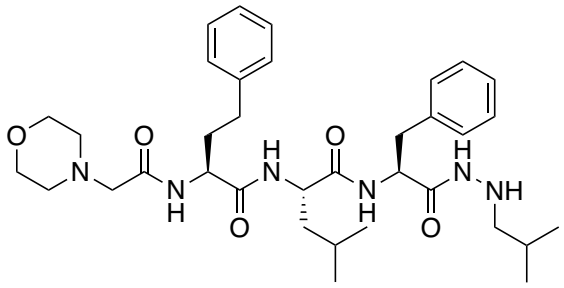
XLIX

RA-1-65. ((*S*)-4-methyl-*N*-((*S*)-1-(2-((*E*)-2-methylpropylidene)hydrazineyl)-1-oxo-3-phenylpropan-2-yl)-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide). Refer to Reductive Amination Procedure – Step 1 for method and work up. Product produced as a white solid. (0.49 g, 0.784 mmols, 99% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8657 (dd, 6H, Leus CH_3), 1.0312 (m, 6H, 2Methyl), 1.3877 (m, 2H, Leu CH_2), 1.5405 (m, 1H, leu, CH), 1.8206-1.8842 (m, CH+ Hphe CH_2), 2.4444 (s+t, CH_2 + Hphe CH_2), 2.9262-3.0046 (m, Phe CH_2 + N-CH_2, 4H), 3.6157 (t, O-CH_2, 4H), 4.3414-4.4178 (m, 2CH, 2H), 5.2199 (q, CH, 1H), 7.1932-7.2569 (M, Phenyls, 10H), 7.3715 (d, NH, 1H), 7.8807 (s, N=CH, 1H), 8.0208 (m, NH, 1H), 8.1990 (d, NH, 1H), 10.9363 (d, NH, 1H). HRMS (ESI) calcd for $[C_{35}H_{50}N_6O_5+H]^+$ 635.3843, 635.4460 (M+1).



L

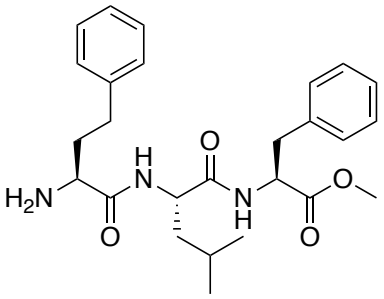
RA-1-66. methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate (2). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white solid. (8.47 g, 15.24 mmols, 81% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: .8655 (dd, Leu CH_3, 6H), 1.4014 (s+q, Leu CH_2+ Boc, 11H), 1.5868 (m, Leu CH, 1H), 1.7929 (m, Hphe CH_2, 2H), 2.5760 (t, HPhe CH_2, 2H), 2.9470-2.9985 (m, Phe CH_2, 2H), 3.6343 (s, OMe, 3H), 3.9053 (m, CH, 1H), 4.3895-4.4617 (m, 2CH, 2H), 7.0377 (d, NH, 1H), 7.1820-7.2747 (m, phenyl, 10H), 7.7384 (d, NH, 1H), 8.3566 (d, NH, 1H). HRMS (ESI) calcd for $[C_{31}H_{43}N_3O_6+Na]^+$ 553.3152, found 576.3530 (M+23).



LI

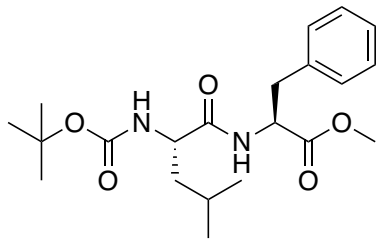
RA-1-67. (*S*)-*N*-((*S*)-1-(2-isobutylhydrazineyl)-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide. Refer to reductive Amination Procedure – Step 2 ($NaCNBH_3$ Reduction) for method and work up. Product produced as a white solid. (0.42 g, 0.662 mmols, 76% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8077 (m, 4Methyls, 12H), 1.4006-1.5233 (m, CH+Leu CH+CH_2, 4H), 1.8402 (q, Hphe CH_2,

2H), 2.3310-2.4537 (t +s, Hphe CH_2+ CH_2+ N-CH_2, 8H), 2.8933-2.9751 (m+d, Phe CH_2+ CH_2, 4H), 3.3227 (t, O-CH_2, 4H), 4.3552 (m, 2CH+NH, 3H), 4.7540 (m, CH, 1H), 7.1769- 7.2689 (m, Phenyls, 10H), 78824 (d, NH, 1H), 8.0868 (d, NH, 1H), 9.2932 (s, NH, 1H). HRMS (ESI) calcd for $[C_{35}H_{52}N_6O_5+H]^+$ 637.3999, found: 637.4570 (M+1).



LII

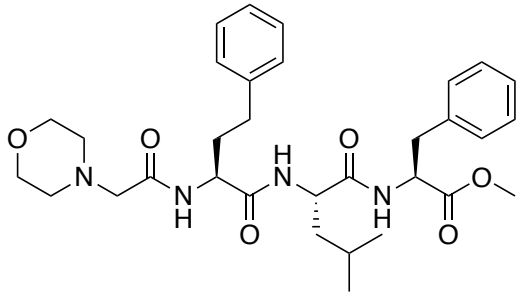
RA-1-68. Methyl ((*S*)-2-amino-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to TFA/DCM deprotection of Boc protecting group procedure for method and work up. Product produced as a white solid. (9.34 g, 15.31 mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: .0.8077.0.9168 (m, Leu CH_3, 6H), 1.4476 (t, Leu CH_2, 2H), 1.6286 (m, Leu CH, 1H), 1.9181 (t, Phe CH_2, 2H), 2.5695 (t, CH_2, 2H), 2.9797-3.0400 (m, CH_2, 2H), 3.5467 (s, OMe, 3H), 3.8845 (s, CH, 1H), 4.4273-4.4877 (m, 2CH, 2H), 7.0813-7.3105 (m, phenyls, 10H), 8.2153 (s, 2NH, 2H), 8.5772 (t, 2NH, 2H). HRMS (ESI) calcd for $[C_{31}H_{43}N_3O_6+H]^+$ 454.2628, found 454.3072 (M+1).



LIII

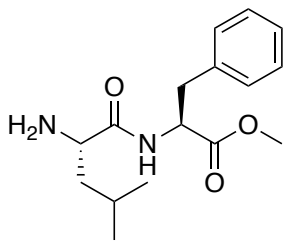
RA-1-69. Methyl (*tert*-butoxycarbonyl)-*L*-leucyl-*L*-phenylalaninate (5). Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white

solid. (14.87 g, 38 mmols, 95% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8619 (m, Leu CH_3, 6H), 1.3133-1.5390 (m, Leu CH+CH_3+ Boc, 12 H), 2.9549-3.0165 (m, Phe CH_2, 2H), 3.5808 (s, OMe, 3H), 3.9707 (q, CH, 1H), 4.4940 (m, CH, 1H), 6.8025 (d, NH, 1H), 7.2232- 7.2642 (m, Phenyl, 5H), 8.1364 (d, NH, 1H). HRMS (ESI) calcd for $[C_{21}H_{32}N_2O_5+Na]^+$ 415.2311, found: 415.2370 (M+23).



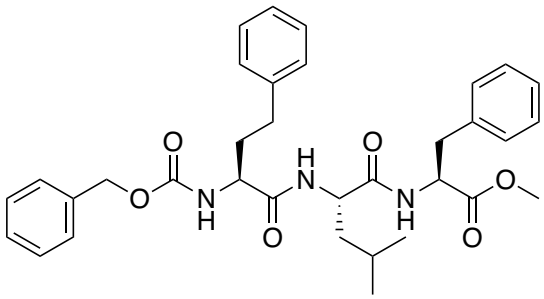
LIV

RA-1-70. Methyl ((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to Morpholine coupling procedure for method and work up. Some fractions were not able to purify completely and were taken to the next step to purify. Product produced as a yellow solid. (3.59 g, 6.08 mmols, 37% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8386-0.8795 (dd, Leu CH_3, 6H), 1.4113 (q, Leu CH_2, 2H), 1.5750 (m, Leu CH, 1H), 1.8102-21.9022 (m, CH_2, 2H), 2.4545 (t, H_2C-N-CH_2, 4H), 2.62 (t, CH_2, 2H), 2. (s, CH_2, 2H), 2.9863-3.1499 (m, CH_2, 2H), 3.2041 (s, OMe, 3H), 3.5386 (t, H_2C-O-CH_2, 4H), 4.3772-4.4692 (m, Alpha-C's, 3H), 7.1896-7.2919 (m, Phenyl, 10H), 7.9951 (d, NH, 1H), 8.0589 (d, NH, 1H), 8.3862 (d, NH, 1H). HRMS (ESI) calcd for $[C_{32}H_{44}N_4O_6+Na]^+$ 603.3261, found 603.3467 (M+23).



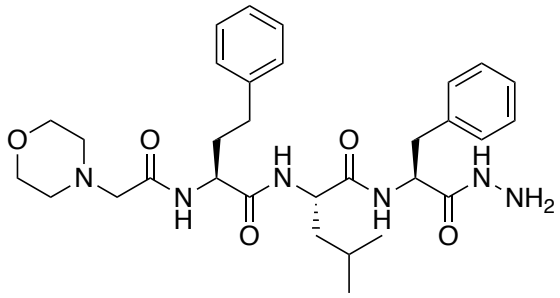
LV

RA-1-71. Methyl *L*-leucyl-*L*-phenylalaninate. Refer to TFA/DCM deprotection of Boc protecting group procedure for method and work up. Product produced as a white solid. (20.51 g, 38 mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.91 (m, Leu CH_3, 6H), 1.54-1.67 (m, Leu CH+CH_2, 3H), 3.07 (m, Phe CH_2, 2H), 3.61 (s, OMe, 3H), 3.80 (q, CH, 1H), 4.57 (q, CH, 1H), 7.30 (m, Phenyl, 5H), 8.16 (s, NH, 3H), 8.98 (d, NH, 1H). HRMS (ESI) calcd for $[C_{16}H_{24}N_2O_3+H]^+$ 293.1787. M/z found: 293.1947 (M+1).



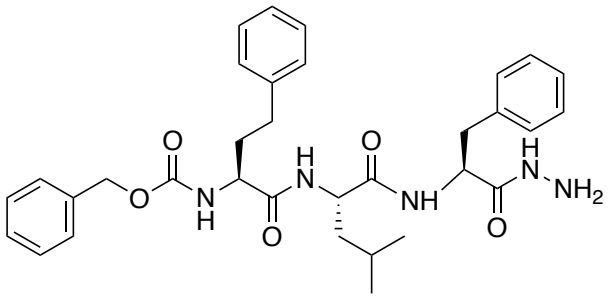
LVI

RA-1-72. Methyl ((*S*)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalaninate. Refer to general NMM and iBCF Coupling procedure for method and work up. Product produced as a white solid. (19.51 g, 33.10 mmols, 84% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8369- 0.8879 (dd, Leu CH_3, 6H), 1.4186 (q, Leu CH_2, 2H), 1.5819 (m, Leu CH, 1H), 1.7758-1.8370 (m, Hphe CH_2, 2H), 2.6228 (t, HPhe CH_2, 2H), 2.9392 (m, Phe CH_2, 2H), 3.5311 (s, OMe, 3H), 4.0210 (m, CH, 1H), 4.3680-4.7400 (m, 2CH, 2H), 5.0416 (s, CH_2, 2H), 7.1847-7.5317 (m, phenyl, 10H), 7.5317 (d, NH, 1H), 7.8787 (d, NH, 1H), 8.3482 (d, NH, 1H). HRMS (ESI) calcd for $[C_{34}H_{41}N_3O_6+Na]^+$ 610.2995, found 610.4361 (M+23).



LVII

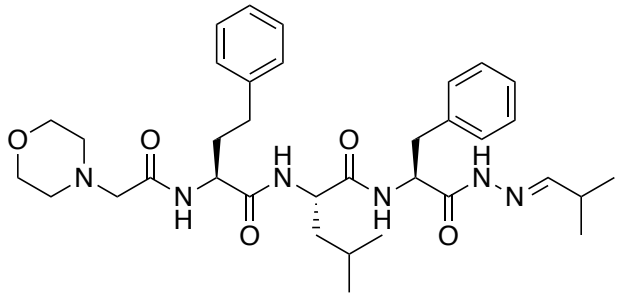
RA-1-73. (*S*)-*N*-((*S*)-1-hydrazineyl-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide. Refer to formation of hydrazide procedure for method and work up. Product produced as a white solid. (1.39 g, 2.31 mmols, 96% yield) with 96% yield. ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8227-0.8747 (dd, Leu CH_3, 6H), 1.3350-1.5204 (m, Leu CH_2+CH, 3H), 1.8432-1.8953 (m, Hph CH_2, 2H), 2.4368 (t, H_2C-N-CH_2, 4H), 2.4992 (t, Hph CH_2, 2H), 2.8221-2.9783 (s+m, CH_2+ Phe CH_2, 4H), 3.6135 (t, H_2C-O-CH_2, 4H), 4.1862 (s, NH_2, 2H), 4.3528-4.4361 (m, 3CH, 3H), 7.0918-7.2790 (m, Phenyls, 10H), 7.8830 (d, NH, 1H), 8.0392 (d, NH, 1H), 9.1014 (s, NH, 1H). HRMS (ESI) calcd for $[C_{31}H_{44}N_6O_5+Na]^+$ 603.3373, found 603.3797 (M+23).



LVIII

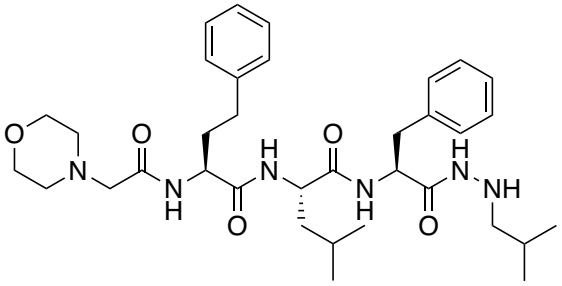
RA-1-74. Benzyl ((*S*)-1-(((*S*)-1-(((*S*)-1-hydrazineyl-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxo-4-phenylbutan-2-yl)carbamate. Refer to formation of hydrazide procedure for method and work up. Product produced as a white solid. (19.38 g, 32.9

mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8182-0.8591 (dd, Leu CH_3, 6H), 1.3909 (q, Leu CH_2, 2H), 1.5443 (m, Leu CH, 1H), 1.7488-1.8306 (m, Hph CH_2, 2H), 2.5977 (m, Hphe CH_2, 2H), 2.8124-2.8943 (m, Phe CH_2, 2H), 4.0295 (q, CH, 1H), 4.1624 (s, NH_2, 2H), 4.3056 (q, CH, 1H), 4.4283 (q, CH, 1H), 5.0624 (s, CH_2, 2H), 7.1692-7.3737 (m, Phenyls, 15H), 7.5578 (d, NH, 1H), 7,8851 (d, NH, 1H), 7.9669 (d, NH, 1H), 9.0816 (s, NH, 1H). HRMS (ESI) calcd for $[C_{33}H_{41}N_5O_5+Na]^+$ 610.3108, found 610.3526 (M+23).



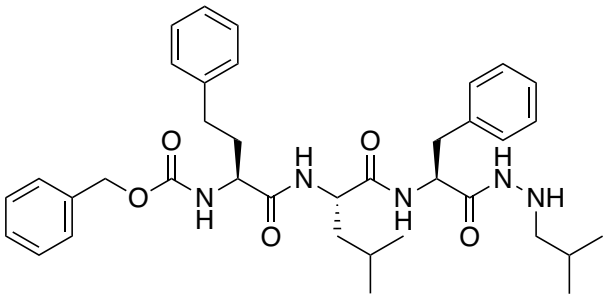
LIX

RA-1-76. (*S*)-*N*-((*S*)-1-(isopropyldiazenyl)-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)pentanamide. Refer to Reductive Amination Procedure – Step 1 for method and work up. Product produced as a white solid. (3.6985 g, 5.80 mmols, 98% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.82-0.89 (m, 6 H, $(CH_3)_2CH$)), 1.04 (m, 6 H, $(CH_3)_2CH$)), 1.41 (m, 2 H, $CH_2CH(CH_3)_2$), 1.55 (m, 1 H, $CH(CH_3)_2$), 1.82-1.91 (m, 2 H, CH_2CH_2CCH), 2.46 (m, 2 H, CH_2CCH), 2.46 (t ,4 H, CH_2NCH_2), 2.82-3.01 (m, 2 H, CH_2CCH), 2.82-3.01 (s, 2 H, CH_2CNH), 3.63 (t, 4H, O-CH_2), 4.38-4.47 (m, 3 H, CHCONH), 7.21-7.25 (m, 10 H, CHCH), 7.38 (d, 1 H, NH), 7.94 (s, 1 H, CHNNH), 8.05 (m, 1 H, NH), 8.21 (d, 1 H, NH), 10.95 (d, 1 H, NH). HRMS (ESI) calcd for $[C_{35}H_{50}N_6O_5+H]^+$ 635.3843, found 635.4311 (M+1).



LX

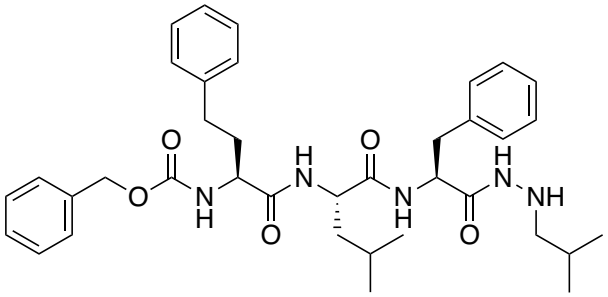
RA-1-77. (*S*)-*N*-((*S*)-1-(2-isobutylhydrazineyl)-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-2-(2morpholinoacetamido)-4-phenylbutanamido)pentanamide. Refer to reductive Amination Procedure – Step 2 ($NaCNBH_3$ Reduction) for method and work up. Product produced as a white solid. (3.53 g, 5.547 mmols, 95% yield). Desired product **2** was obtained as a white solid with 95% yield. ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.82-0.89 (m, 12 H, $(CH_3)_2CH$)), 1.40 (m, 2 H, $CH_2CH(CH_3)_2$), 1.54 (m, 1 H, $CH(CH_3)_2$), 1.83 (m, 2 H, CH_2CHCH), 2.34 (m, 2 H, CH_2NHNH), 2.39 (t,4 H, CH_2N), 2.85-2.98 (m, 2 H, CH_2CCH), 2.85-2.98 (s, 2 H, CH_2CNH), 3.61 (t, 4H, O-CH_2), 4.32-4.43 (m, 3 H, CHCONH), 4.76 (m, 1 H, NHNH), 7.12 (m, 1 H, NH), 7.18-7.28 (m, 10 H, CHCH), 7.89 (d, 1 H, NH), 8.05 (d, 1 H, NH), 9.30 (d, 1 H, NH). HRMS (ESI) calcd for $[C_{35}H_{52}N_6O_5+H]^+$ 637.3999, found 637.4449 (M+1).



LXI

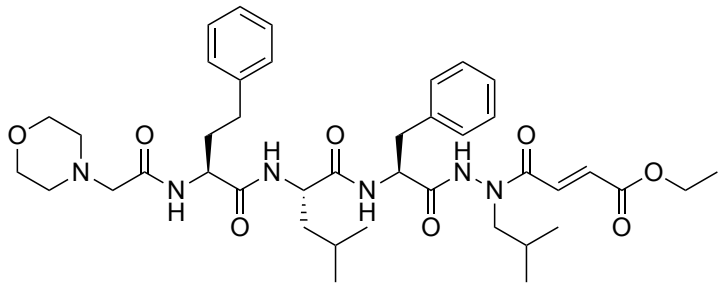
RA-1-78-1. Benzyl ((*S*)-1-(((*S*)-1-(((*S*)-1-(2-isobutylhydrazineyl)-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxo-4-phenylbutan-2-yl)carbamate. Refer to

reductive Amination Procedure – Step 2 ($NaCNBH_3$ Reduction) for method and work up. Product produced as a white solid. (9.50 g, 14.58 mmols, 90% yield). ^1H NMR (DMSO-d_6, 400MHz) δ: 0.79-0.87 (m, 12 H, $(CH_3)CH$), 1.40-1.57 (m. 2 H, $CH(CH_3)$) 1.40-1.57 (m, 2 H, $CHCH_2$),1.80-1.88 (m, 2 H, CH_2CH), 2.33 (quin, 2 H, CH_2NH), 2.63 (m, 2 H, CH_2CCH), 2.83-2.90 (m, 2 H, CH_2CCH), 4.03 (q, 1 H, CHCO), 4.33 (q, 1 H, CHCO), 4.43 (q, 1 H, CHCO), 4.76 (s, 1 H, NHNH), 5.05 (s, 2 H, O-CH_2), 7.12-7.37 (m, 15 H, CHCH), 7.76 (d, 1 H, NH), 7.91 (d, 1 H, NH), 8.04 (d, 1 H, NH), 9.31 (d, 1 H, NH). HRMS (ESI) calcd for $[C_{37}H_{49}N_5O_5+Na]^+$ 666.3734, found: 666.4239 (M+23).



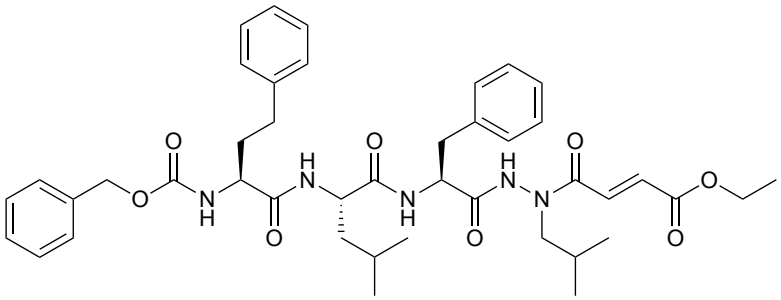
LXII

RA-1-78-2. Benzyl ((*S*)-1-(((*S*)-1-(((*S*)-1-(2-isobutylhydrazineyl)-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxo-4-phenylbutan-2-yl)carbamate. Refer to reductive Amination Procedure – Step 2 ($NaCNBH_3$ Reduction) for method and work up. Product produced as a white solid. (8.74 g, 13.61 mmols, 93% yield). ^1H NMR (DMSO-d_6, 400MHz) δ: 0.80-0.87 (m, 12 H, $(CH_3)CH$), 1.40-1.57 (m. 2 H, $CH(CH_3)$) 1.40-1.57 (m, 2 H, $CHCH_2$),1.81-1.88 (m, 2 H, CH_2CH), 2.33 (quin, 2 H, CH_2NH), 2.64 (m, 2 H, CH_2CCH), 2.83-2.92 (m, 2 H, CH_2CCH), 4.02 (q, 1 H, CHCO), 4.34 (q, 1 H, CHCO), 4.44 (q, 1 H, CHCO), 4.76 (m, 1 H, NHNH), 5.06 (s, 2 H, O-CH_2), 7.11-7.38 (m, 15 H, CHCH), 7.56 (d, 1 H, NH), 7.92 (d, 1 H, NH), 8.06 (d, 1 H, NH), 9.32 (d, 1 H, NH). HRMS (ESI) calcd for $[C_{37}H_{49}N_5O_5+Na]^+$ 666.3734, found 666.2448 (M+23).



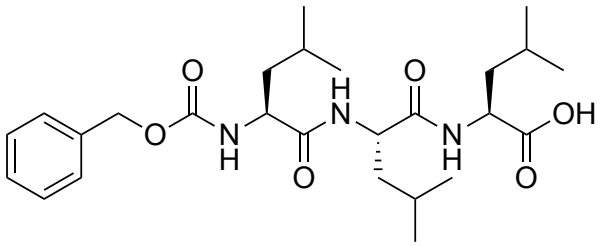
LXIII

RA-1-79. Ethyl (*E*)-4-(1-isobutyl-2-(((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalanyl)hydrazineyl)-4-oxobut-2-enoate. Refer to Aza-peptide Michael acceptor inhibitor synthesis coupling procedure for method and work up. Product produced as a yellow solid. (142.3 mg, 0.186 mmols, 59% yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.6671-0.8438 (m, 12 H, $(CH_3)_2CH$), 1.1902 (m, 3 H, O-CH_3), 1.4085-1.5552 (m, 4 H, CH_2CH), 1.8216 (m, 2 H, CH_2CCH), 2.4385 (t, 4 H, CH_2NCH_2), 2.4985 (m, 2 H, CH_2CH_2C), 2.9511 (m, 2 H, CH_2CCH), 2.9731 (s, 2 H, CH_2), 3.6013 (t, 4 H, O-CH_2), 4.1418 (m, 2 H, CHCO), 4.3651 (s, 2 H, O-CH_2), 4.5574 (q, 1 H, CHCO), 6.5400-6.5786 (d, 1 H, CHCH), 7.1581 (m, 1 H, CHCH), 7.1581-7.2452 (m, 10H, CHCHCH), 7.8933 (d, 1 H, NH), 7.9986 (s, 1 H, NH), 8.4256 (d, 1 H, NH), 10.7274 (s, NH, 1 H). HRMS (ESI) calcd for $[C_{41}H_{58}N_6O_8+H]^+$ 764.4316, found 763.4182(M+1).



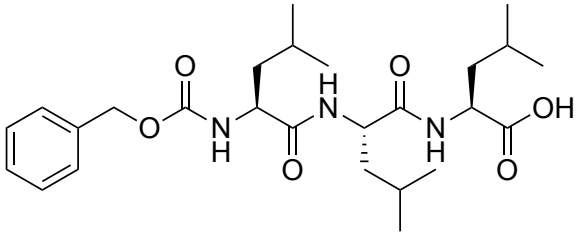
LXIV

RA-1-80. Ethyl (*E*)-4-(2-(((*S*)-2-(((benzyloxy)carbonyl)amino)-4-phenylbutanoyl)-*L*-leucyl-*L*-phenylalanyl)-1-isobutylhydrazineyl)-4-oxobut-2-enoate. Refer to Aza-peptide Michael acceptor inhibitor synthesis coupling procedurefor method and work up. Product produced as a white solid. (80 mg, 0.104 mmols, 16% yield).Yield: 16%. ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8077. 0.68-0.86 (m, 12 H, $(CH_3)_2CH$), 1.22 (m, 3 H, CH_3CH_2), 1.41-1.56 (m, 4 H, $CH_2(CH_3)_2$+CH_2), 1.81 (m, 2 H, CH_2CCH), 2.64 (m, 2 H, CH_2CH_2CCH), 2.93 (s, 2 H, CH_2CH), 4.04 (q, 1 H, CHCO), 4.16 (d, 2 H, O-CH_2), 4.37 (m, 1 H, CHCO), 4.55 (q, 1 H, CHCO), 5.05 (s, 2 H, CH_2OCO), 6.60 (d, 1 H, CHCH), 7.18-7.56 (m, 16 H, CCHCH+CHCH), 7.84 (s, 1 H, NH), 7.94 (s, 1 H, NH), 8.41 (d, 1 H, NH), 10.75 (s, 1 H, NH). HRMS (ESI) calcd for $[C_{43}H_{55}N_5O_8+H]^+$ 770.4051, found 770.3897 (M+1).



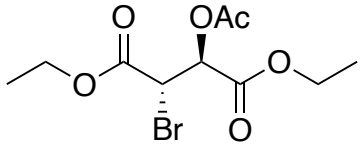
LXV

RA-1-83. ((Benzyloxy)carbonyl)-*L*-leucyl-*L*-leucyl-*L*-leucine. Refer to Solid phase peptide synthesis procedure for method and work up. (0.0786 g, 0.16 mmols, quantitative yield). Product produced as a white solid. ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8291 (m, 6-Leu's CH_3, 18H), 1.4216-1.6118 (m, CH_2+CH+CH, 9H), 4.0357 (q, CH, 1H), 4.2088 (q, CH, 1H), 4.4387 (q, CH, 1H), 5.0213 (s, CH_2,2H), 7.33455-7.4088 (m, phenyl+ NH, 6H), 7.8849 (d, NH, 1H), 8.0015 (d, NH, 1H). HRMS (ESI) calcd for $[C_{26}H_{41}N_3O_6+H]^+$ 492.2995, found 492.3059 (M+1), and 983.6047 (2M+1).



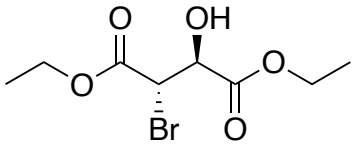
LXVI

RA-1-84. ((Benzyloxy)carbonyl)-*L*-leucyl-*L*-leucyl-*L*-leucine . Refer to Solid phase peptide synthesis procedure for method and work up. Product produced as a white solid. (0.784 g, 1.60 mmols, quantitative yield). ^{1}H NMR (DMSO-d_6, 400MHz) δ: 0.8455-0.8748 (m, 6-Leu's CH_3, 18H), 1.4248-1.6120 (m, CH_2+CH+CH, 9H), 4.0403 (q, CH, 1H), 4.2129 (q, CH, 1H), 4.3562 (q, CH, 1H), 5.0174 (s, CH_2,2H), 7.3433-7.3989 (m, phenyl+ NH, 6H), 7.8816 (d, NH, 1H), 7.9957 (d, NH, 1H). HRMS (ESI) calcd for $[C_{26}H_{41}N_3O_6+H]^+$ 492.2995, found 492.3058 (M+1).



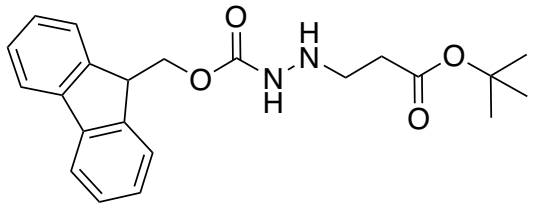
LXVII

RA-1-89. Diethyl 2-acetoxy-3-bromosuccinate. Refer to epoxide warhead synthesis Step 1 (bromination) for method and work up. Product produced as a yellow oil. (4.85 mmols, yield calculated over two steps RA-1-91) HRMS (ESI) calcd for $[C_{10}H_{15}BrO_6+H]^+$ 311.0052, found 311.0149 (M+1).



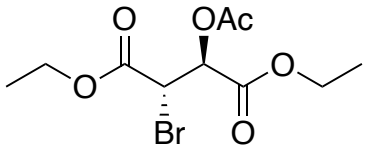
LXVIII

RA-1-91. Diethyl 2-bromo-3-hydroxysuccinate. Refer to epoxide warhead synthesis Step 2 (acetoxy to hydroxy group) for method and work up. Product produced as a as a yellow oil. (0.4314 g, 1.60 mmols, 33% yield) ^{1}H NMR ($CDCl_3$, 400MHz): 1.3064 (m, 6H, CH_3), 4.2884 (m, 4H, CH_2), 4.6831 (d, 1H, CH), 4.7269 (d, 1H, CH). HRMS (ESI) calcd for $[C_8H_{14}BrO_5+Na]^+$ 290.9946, found 290.9952 (M+23).



LXIX

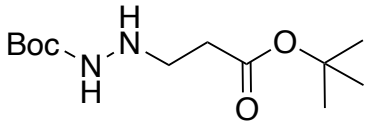
RA-1-92. (9*H*-fluoren-9-yl)methyl 2-(3-(*tert*-butoxy)-3-oxopropyl)hydrazine-1-carboxylate . Refer to aza-Gln side chain synthesis (step 1) for method and work up. Product produced as a white solid. (0.2038 g, 522.93 µm, 13% yield). ^{1}H NMR (DMSO-d_6, 400MHz): 1.4086 (s, 9H, CH_3), 2.2933 (t, 2H, CH_2), 2.8846 (d, 2H, CH_2), 4.2294 (m, 1H, NH), 4.3084 (d, 2H, CH_2), 4.6187 (s, 1H, NH), 7.3516 (m, 2H, CH), 7.4278 (m, 2H, CH), 7.6882 (m, 2H, CH), 7.8855 (m, 2H, CH), 8.6956 (s, 1H, NH). HRMS (ESI) calcd for $[C_{22}H_{26}N_2O_4+H]^+$ 382.1893, found 383.1930 (M+1).



LXX

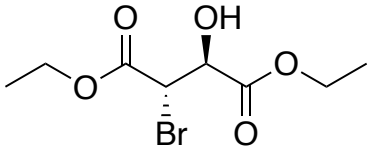
RA-1-100. Diethyl 2-acetoxy-3-bromosuccinate . Refer to epoxide warhead synthesis Step 1 (bromination) for method and work up. Product produced as a yellow oil. (13.68 g, 43.9 mmols, 90% yield). ^{1}H NMR ($CDCl_3$, 400MHz): 1.3085 (m, 6H, CH_3), 2.1770 (s, 3H, CH_3), 4.2896 (m,

4H, CH_2), 4.7996 (d, 1H, CH), 5.6065 (d, 1H, CH). HRMS (ESI) calcd for $[C_{10}H_{15}BrO_6+H]^+$ 311.0052, found 311.0165 (M+1).



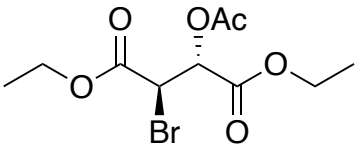
LXXI

RA-1-101. *Tert*-butyl 2-(3-(*tert*-butoxy)-3-oxopropyl)hydrazine-1-carboxylate. Refer to aza-Gln side chain synthesis (step 1) for method and work up. DIPEA was added via syringe pump at a rate of 150 µL/hour. Product produced as a white solid. (90 mg, 0.34 mmols, 3.4% yield). ^{1}H NMR ($CDCl_3$, 400MHz): 1.3894 (m, 18H, CH_3), 2.5361 (t, 2H, CH_2), 3.2165 (t, 2H, CH_2). HRMS (ESI) calcd for $[C_{12}H_{24}N_2O_4+H]^+$ 260.1736, found 261.1804 (M+1).



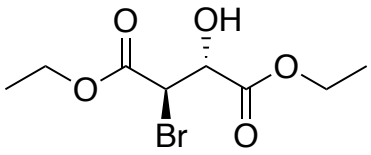
LXXII

RA-1-102. Diethyl 2-bromo-3-hydroxysuccinate . Refer to epoxide warhead synthesis Step 2 (acetoxy to hydroxy group) for method and work up. Product produced as a clear oil (7.13 g, 26.7 mmols, 60% yield). ^{1}H NMR ($CDCl_3$, 400MHz): 1.3271 (m, 6H, CH_3), 4.2915 (m, 4H, CH_2), 4.6708 (d, 1H, CH), 4.7256 (d, 1H, CH). HRMS (ESI) calcd for $[C_8H_{14}BrO_5+H]^+$ 267.9946, found 269.0045 (M+1).



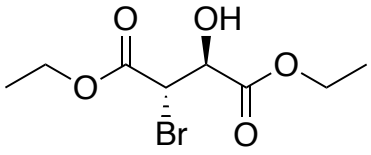
LXXIII

RA-1-105. Diethyl 2-acetoxy-3-bromosuccinate. Refer to epoxide warhead synthesis Step 1 (bromination) for method and work up. Product produced as a yellow oil. (13.17 g, 42.3 mmols, 87% yield). ^{1}H NMR ($CDCl_3$, 400MHz): 1.3285 (m, 6H, CH_3), 2.2042 (s, 3H, CH_3), 4.3071 (m, 4H, CH_2), 4.7300 (d, 1H, CH), 4.8611 (d, 1H, CH). HRMS (ESI) calcd for $[C_{10}H_{15}BrO_6+H]^+$ $[C_{31}H_{43}N_3O_6+H]^+$ 268.9954, found 269.0004 (M+1).



LXXIV

RA-1-107. Diethyl 2-bromo-3-hydroxysuccinate. Refer to epoxide warhead synthesis Step 2 (acetoxy to hydroxy group) for method and work up. Product produced as a yellow oil. (10.12 g, 37.9 mmols, 88% yield). ^{1}H NMR ($CDCl_3$, 400MHz): 1.3390 (m, 6H, CH_3), 3.4432 (d, 1H, OH), 4.2832 (m, 4H, CH_2), 4.6907 (t, 1H, CH), 4.7240 (d, 1H, CH). HRMS (ESI) calcd for $[C_{31}H_{43}N_3O_6+H]^+$ 268.9954, found 269.0004 (M+1).

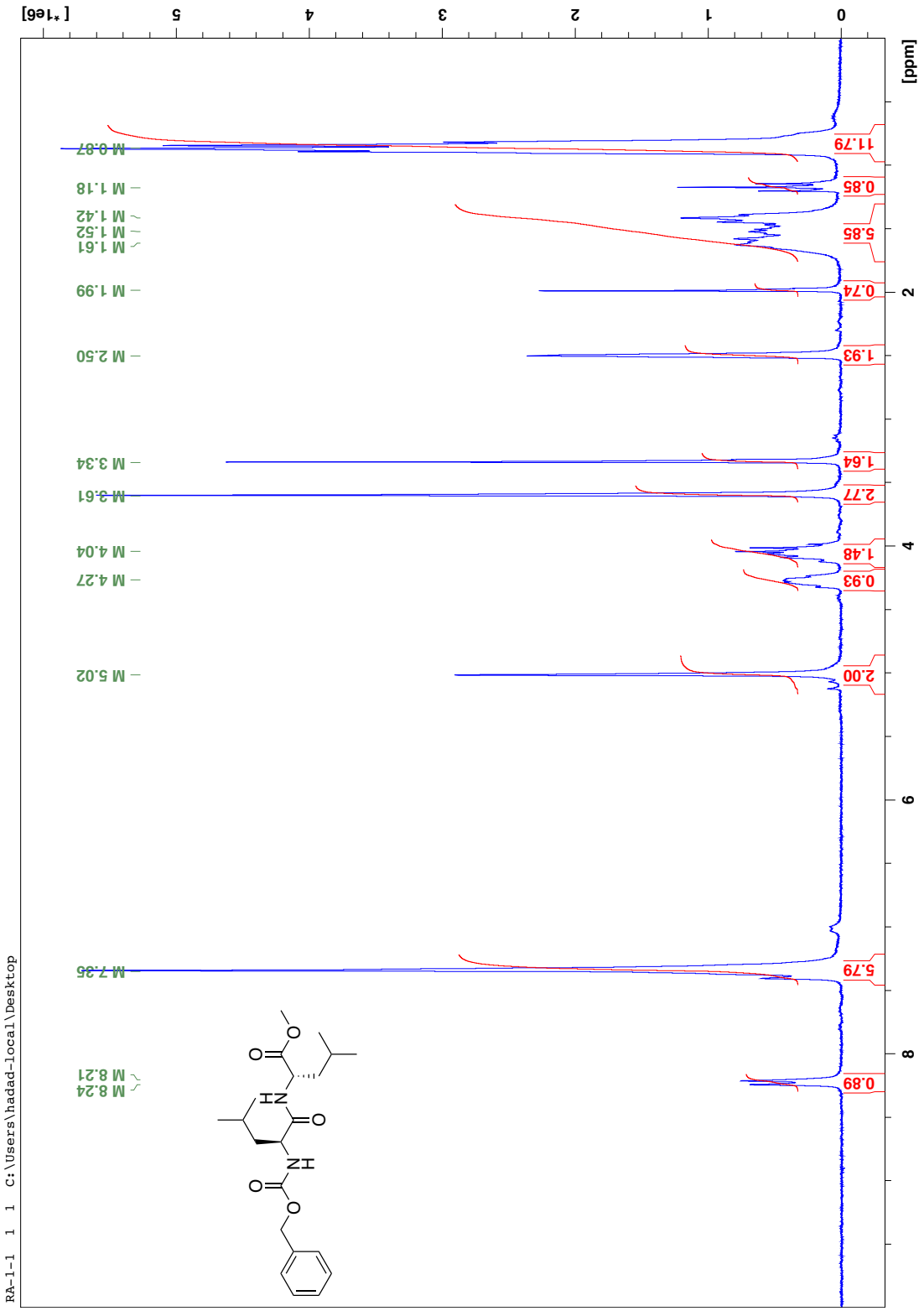


LXXV

RA-1-113. Diethyl 2-bromo-3-hydroxysuccinate. Refer to epoxide warhead synthesis Step 2 (acetoxy to hydroxy group) for method and work up. Product produced as a clear oil. (2.87 g, 10.68 mmols, 55%yiled). ^{1}H NMR ($CDCl_3$, 400MHz): 1.3336 (m, 6H, CH_3), 3.4456 (d, 1H, OH), 4.2976 (m, 4H, CH_2), 4.6957 (t, 1H, CH), 4.7223 (d, 1H, CH). HRMS (ESI) calcd for $[C_{31}H_{43}N_3O_6+Na]^+$ 290.9946, found 290.9836 (M+23).

APPENDIX A

^{1}H NMR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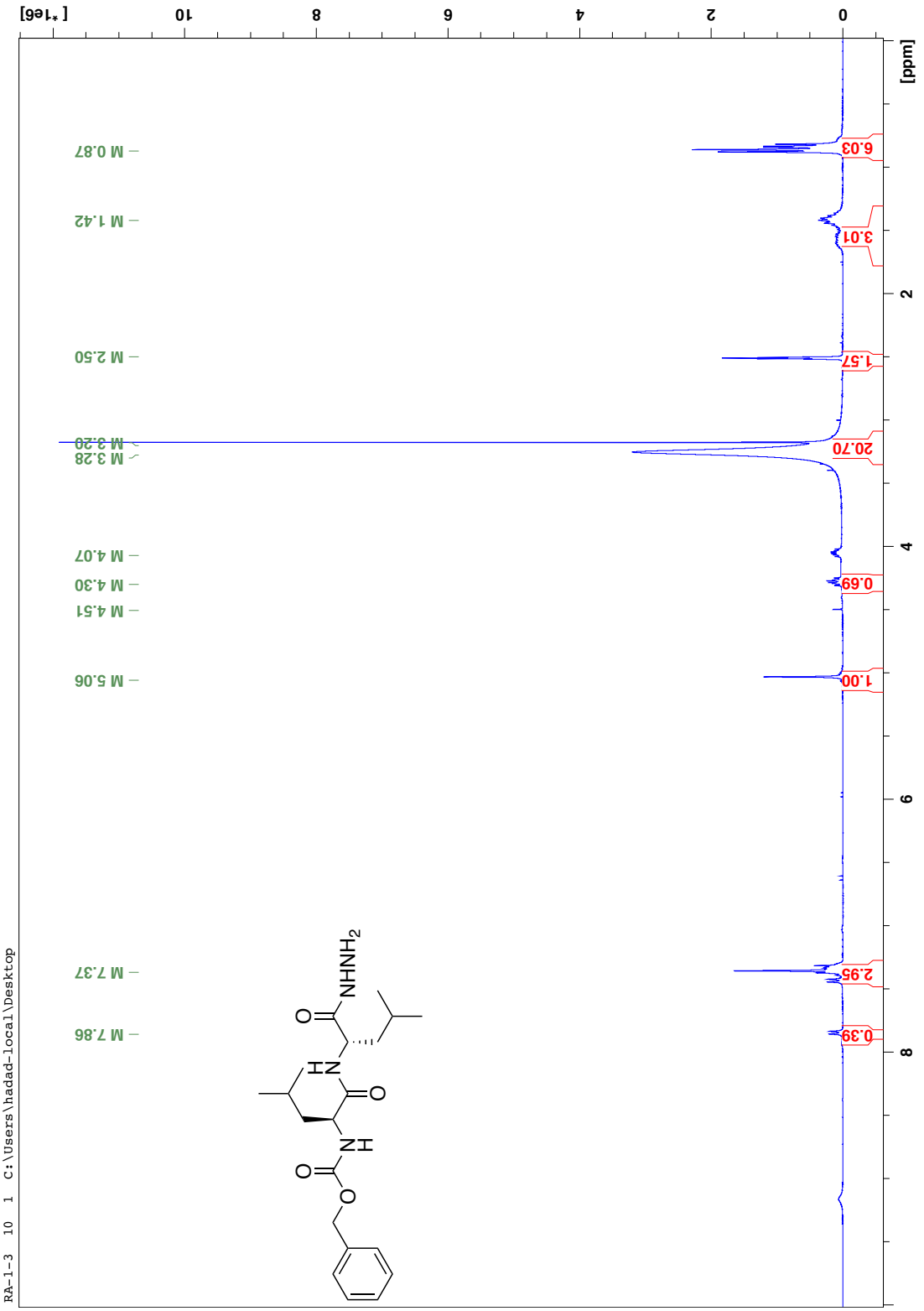
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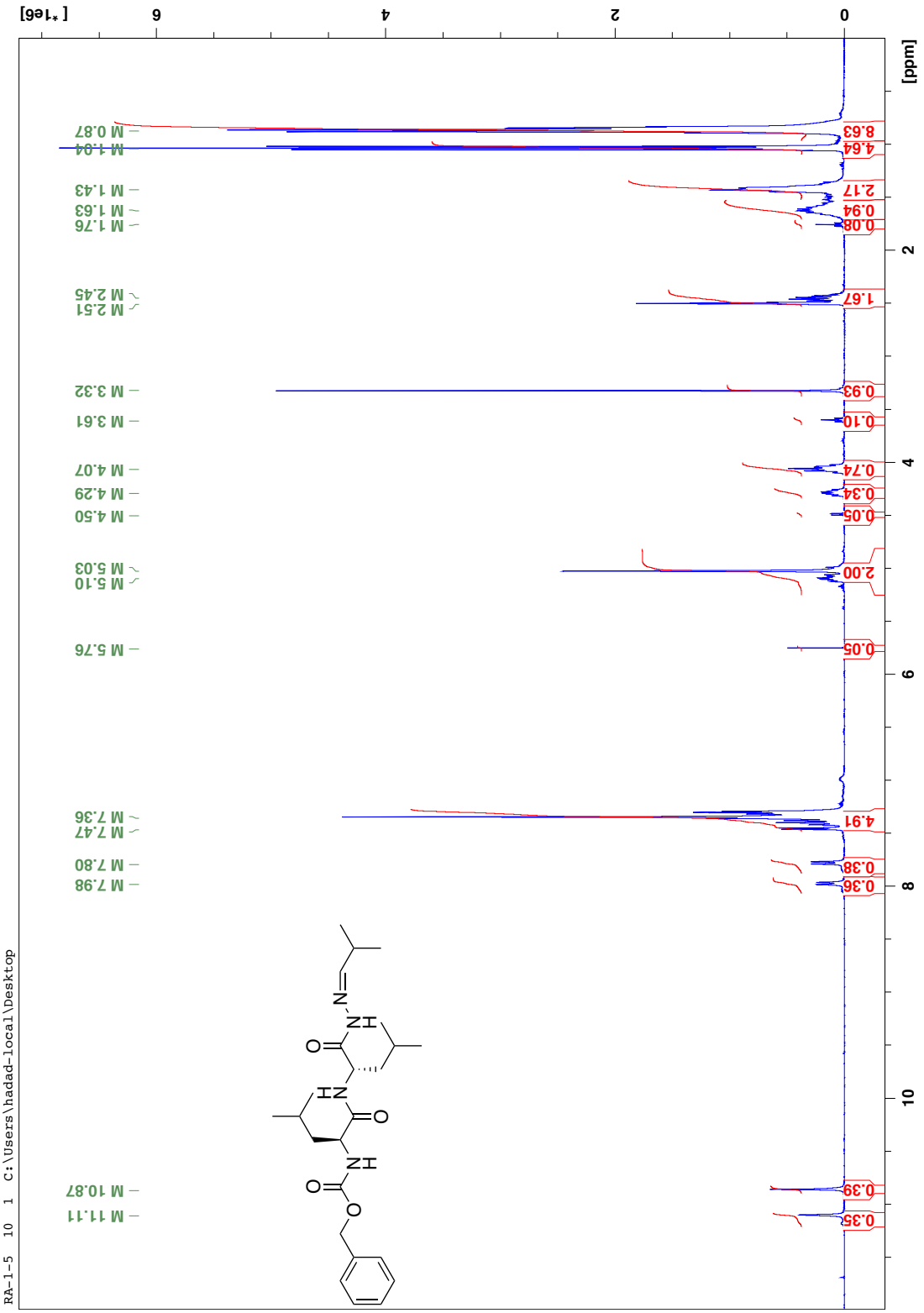
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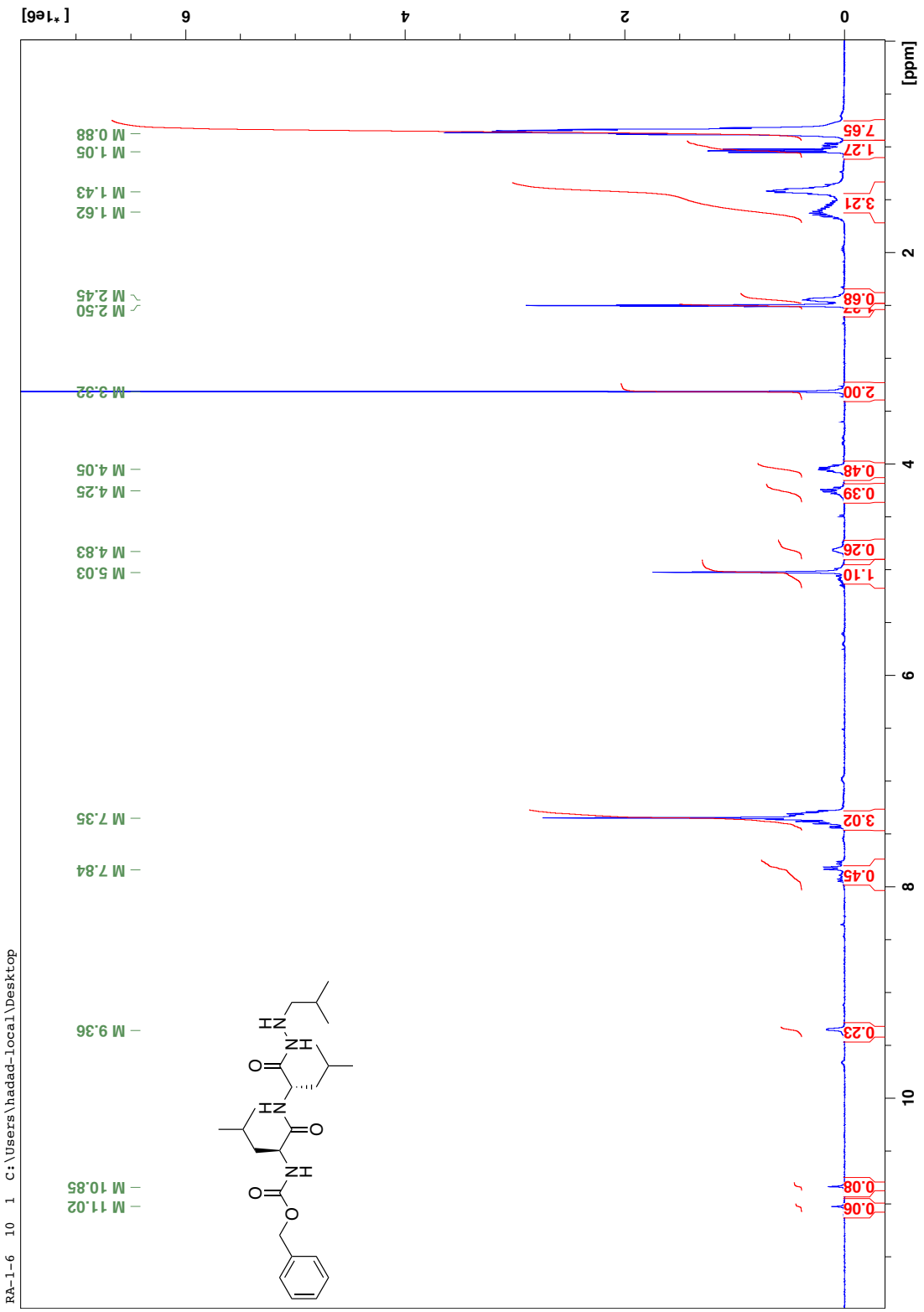
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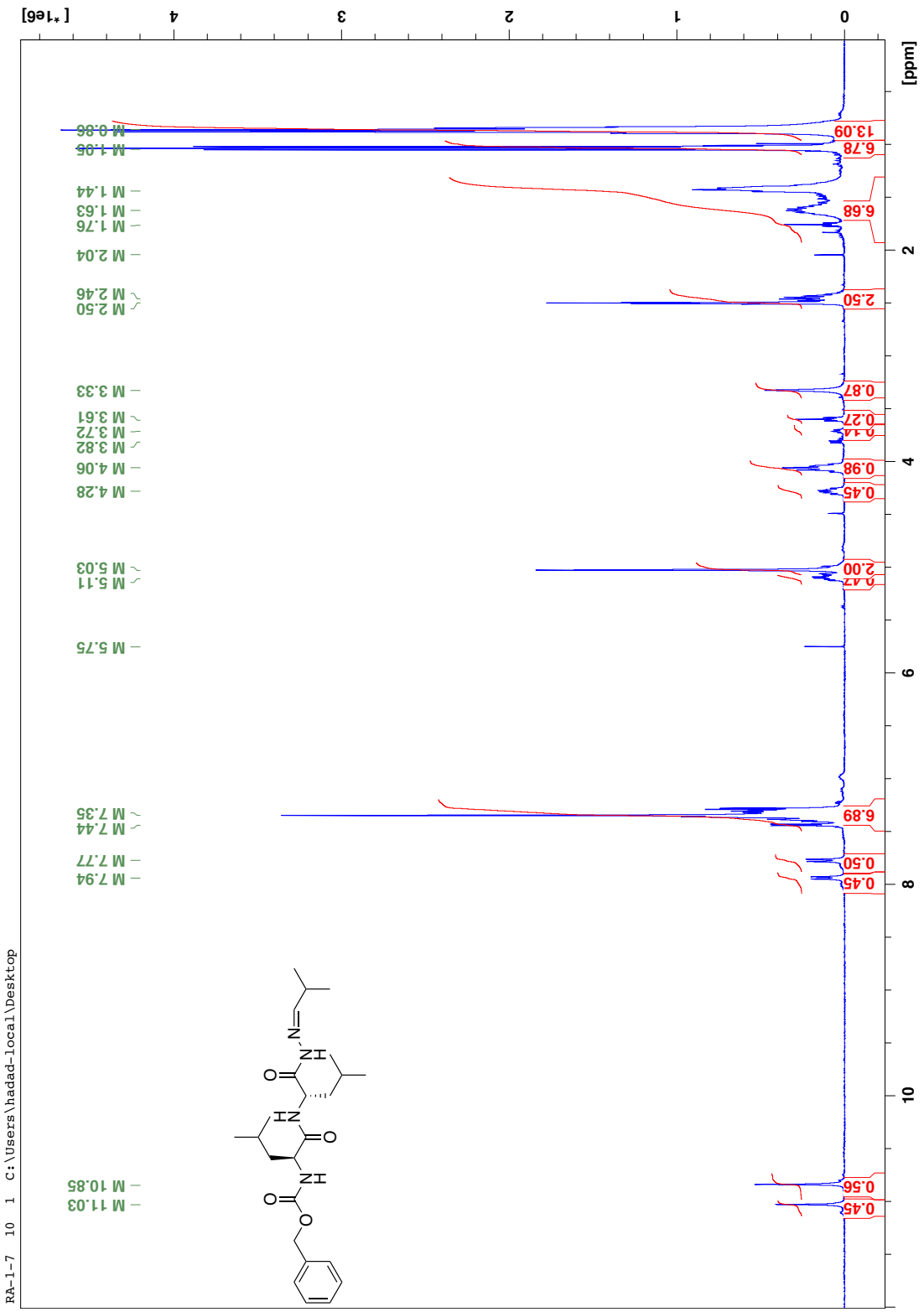
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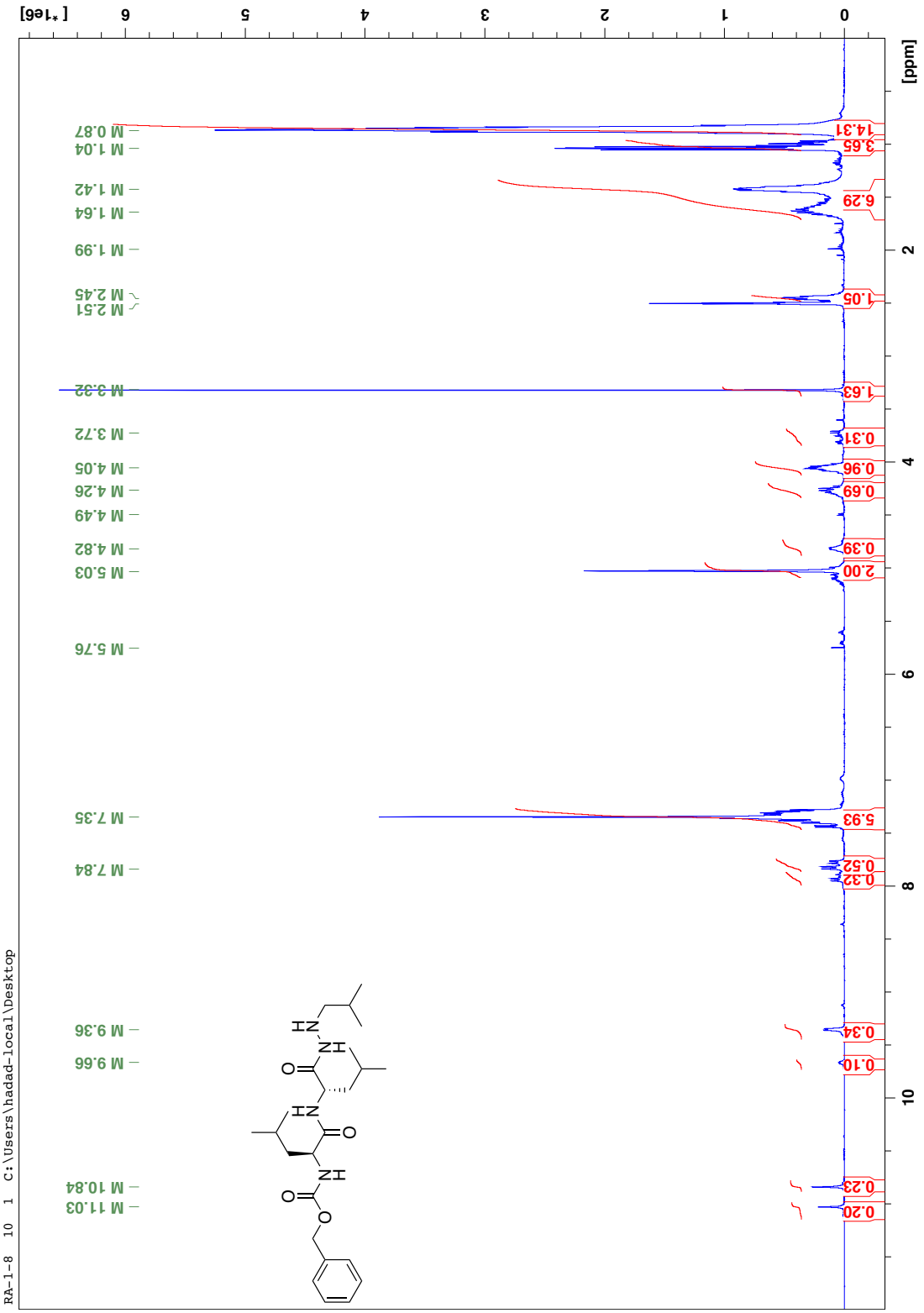
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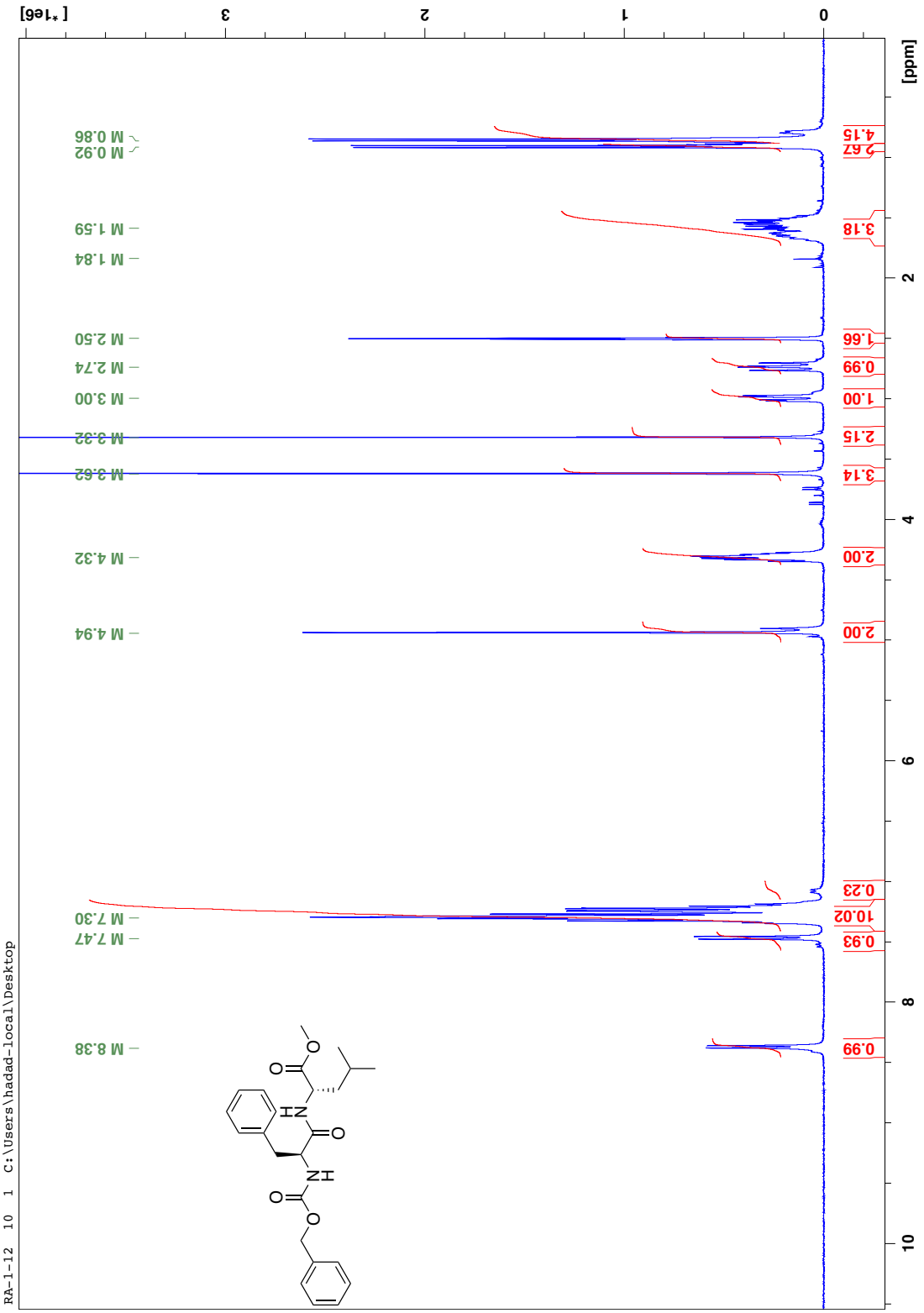
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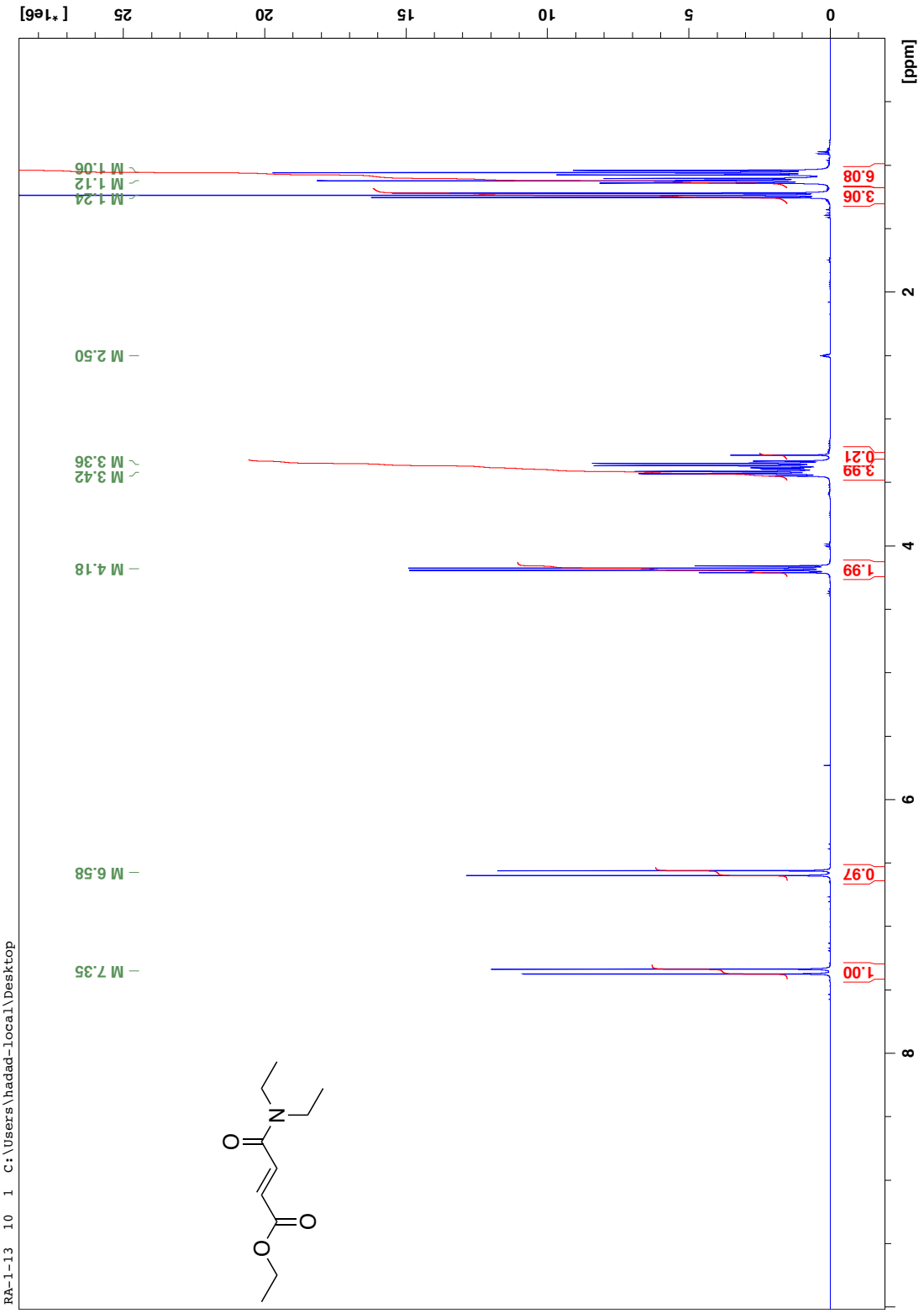
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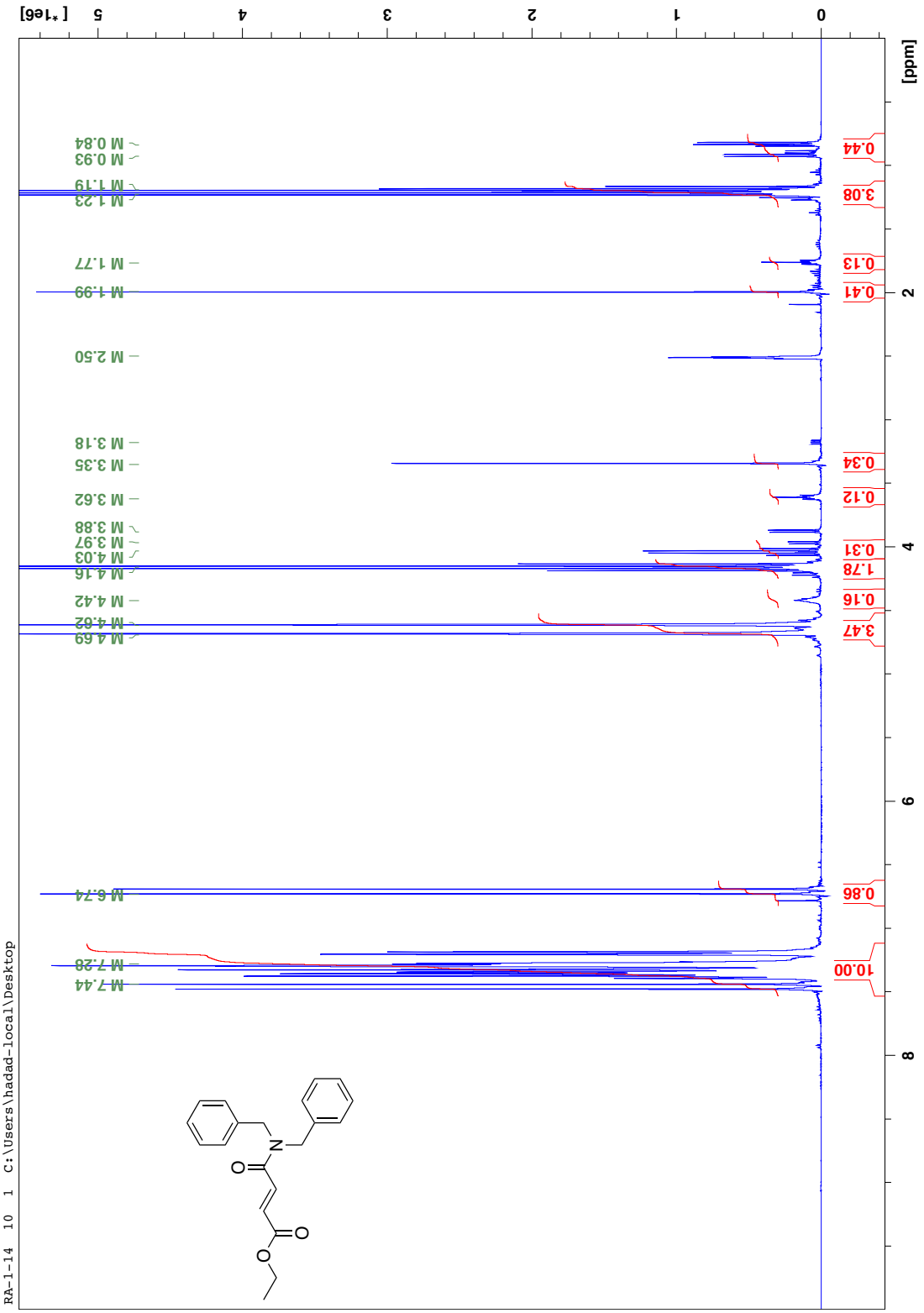
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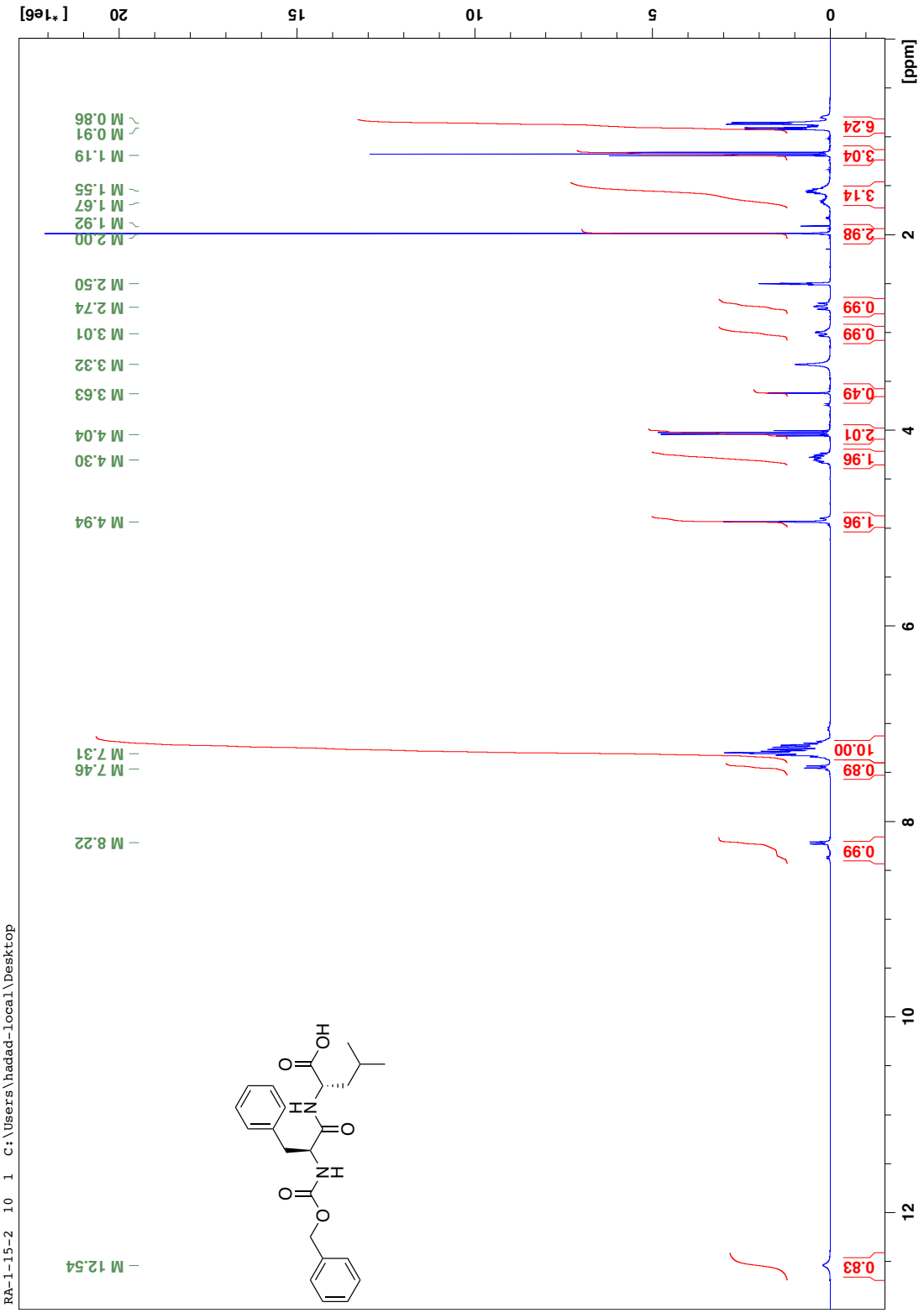
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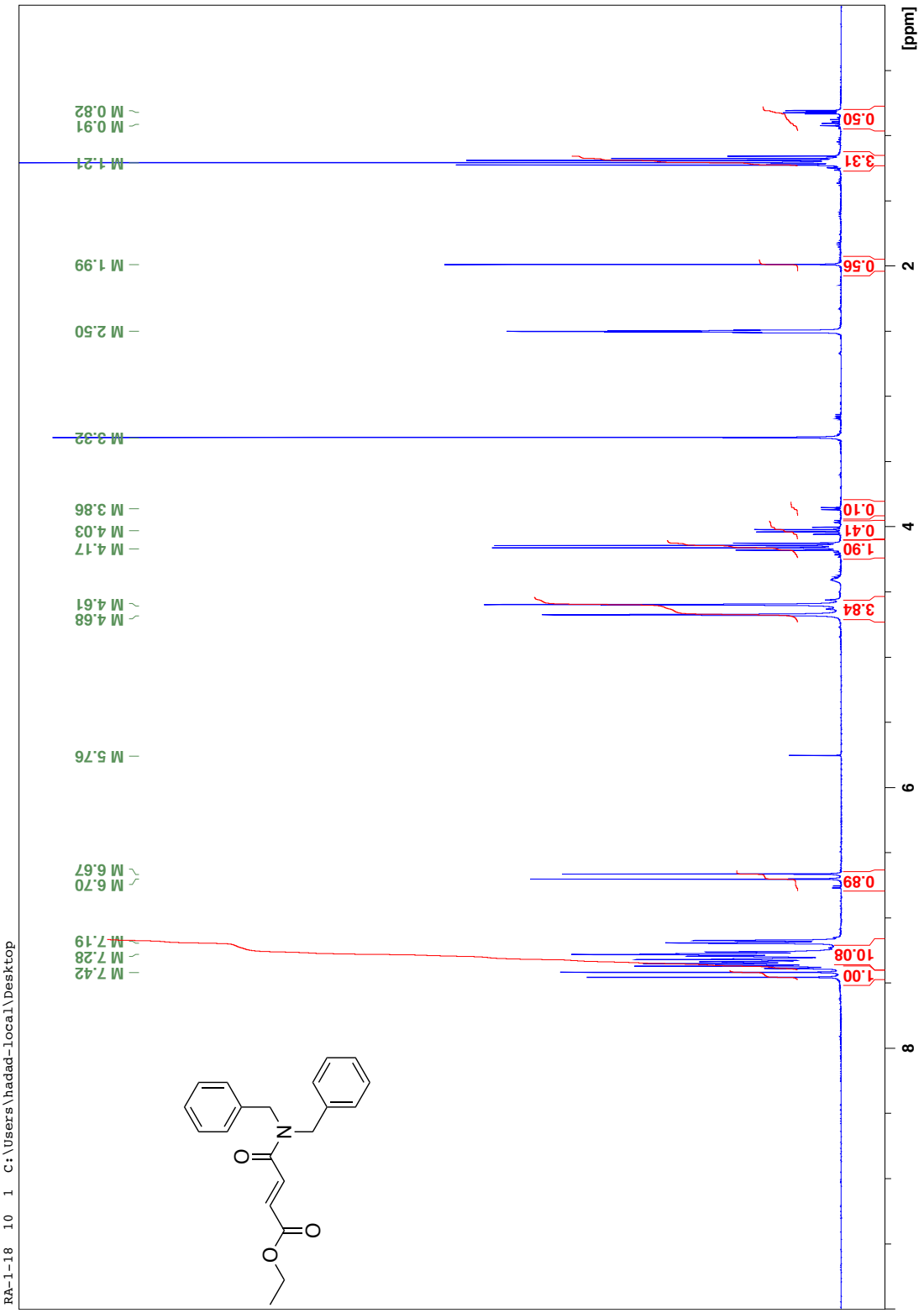
M 1.92
M 1.67
M 1.55
M 1.19
M 0.91
M 0.86


RA-1-18 10 1 C:\Users\hadad-local\Desktop
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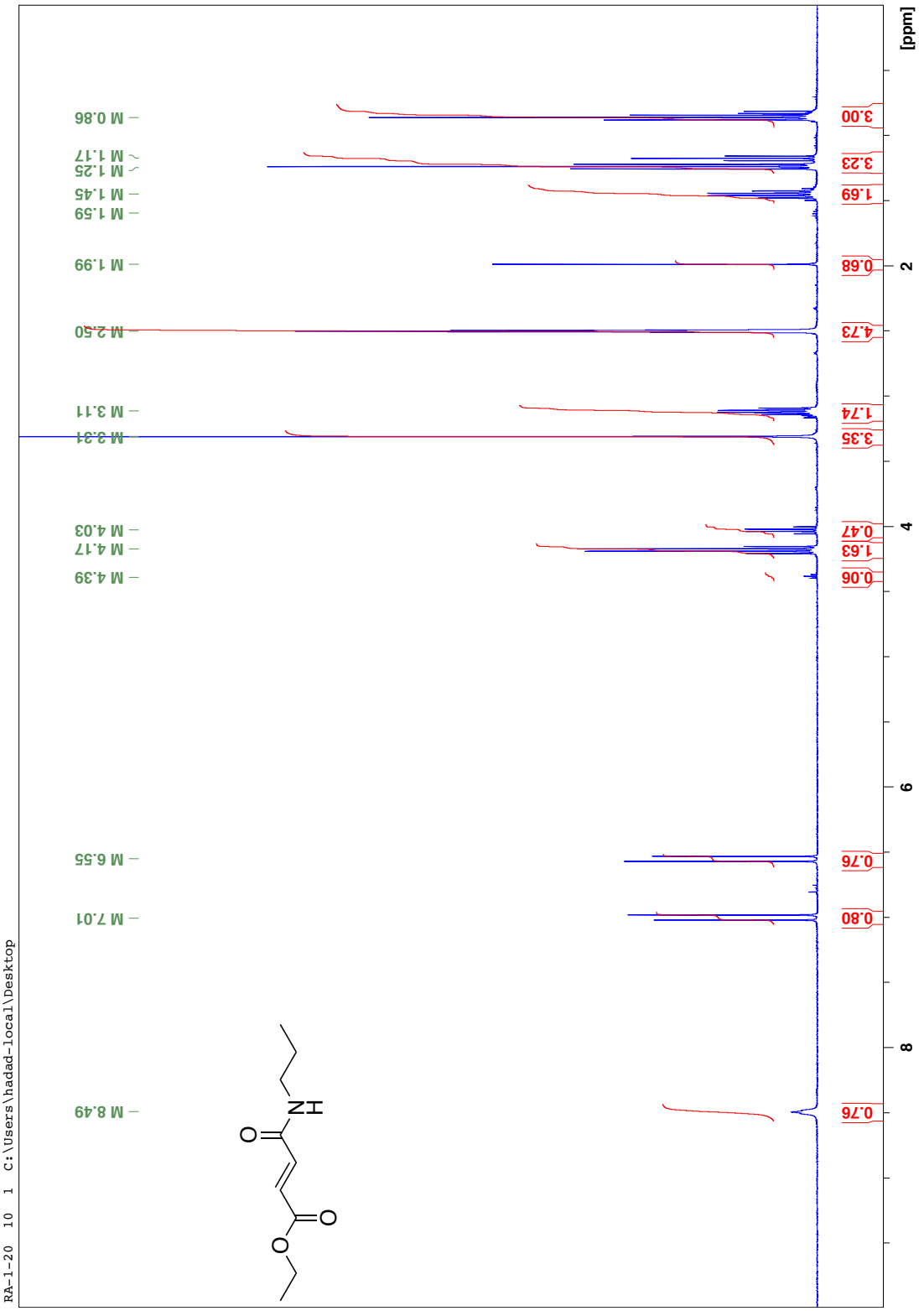
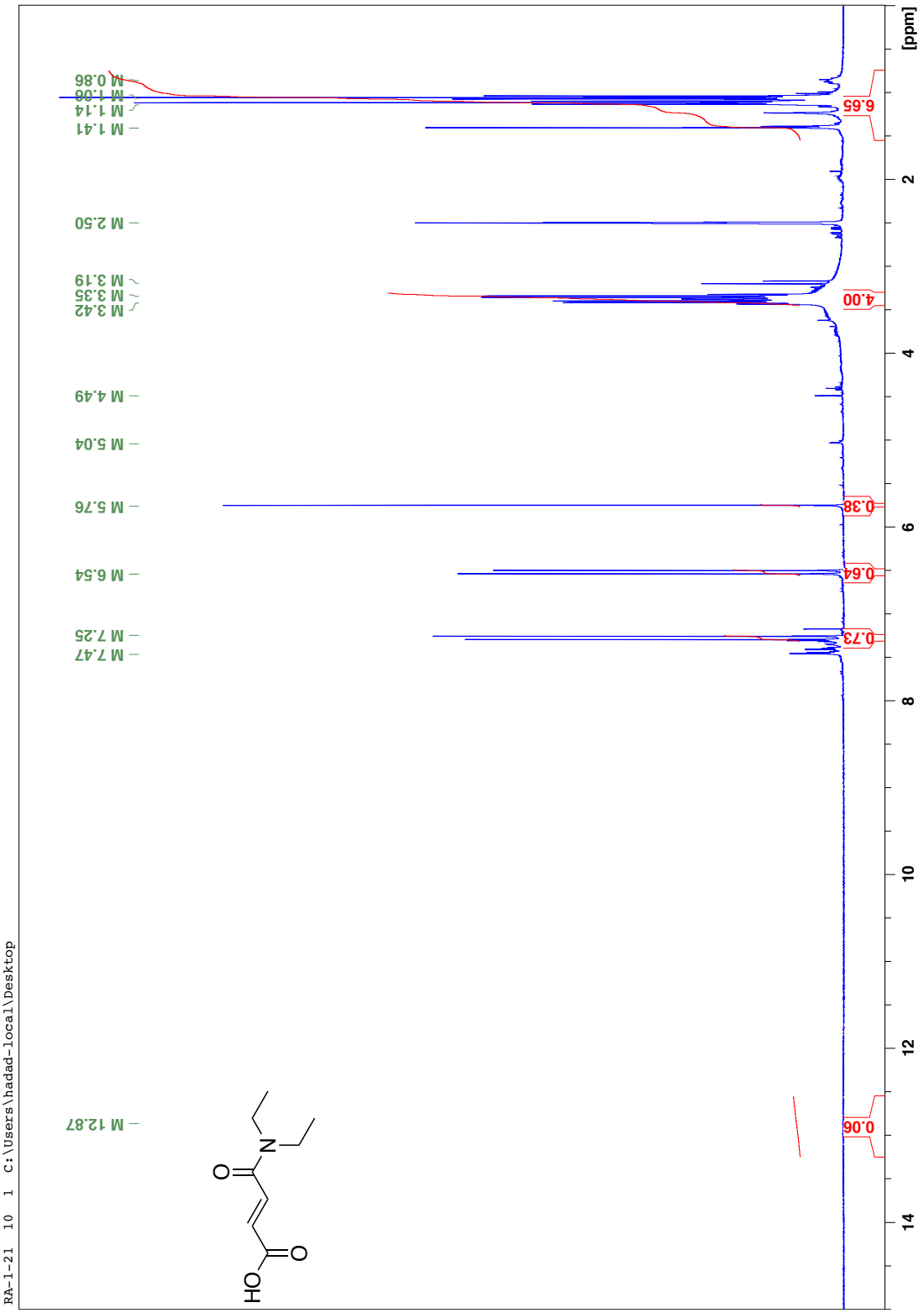
4
6
8
0.50
3.31
0.56
1.90
0.10
0.41
3.84
0.89
10.08
1.00
M 0.82
M 0.91
M 1.21
M 1.99
M 2.50
M 3.32
M 3.86
M 4.03
M 4.17
M 4.61
M 4.68
M 5.76
M 6.67
M 6.70
M 7.19
M 7.28
M 7.42
O
N
O
O
O


RA-1-20 10 1 C:\Users\hadad-local\Desktop
M 8.49
M 7.01
M 6.55
M 4.39
M 4.17
M 4.03
M 3.31
M 3.11
M 2.50
M 1.99
M 1.59
M 1.45
M 1.25
M 1.17
M 0.86
0.76
0.80
0.76
0.06
1.63
0.47
3.35
1.74
4.73
0.68
1.69
3.23
3.00
[ppm]
2
4
6
8
O
O
O
N
H


RA-1-21 10 1 C:\Users\hadad-local\Desktop
M 12.87
M 7.47
M 7.25
M 6.54
M 5.76
M 5.04
M 4.49
M 3.42
M 3.35
M 3.19
M 2.50
M 1.41
M 1.14
M 1.06
M 0.86
6.65
4.00
0.38
0.64
0.73
0.06
[ppm]
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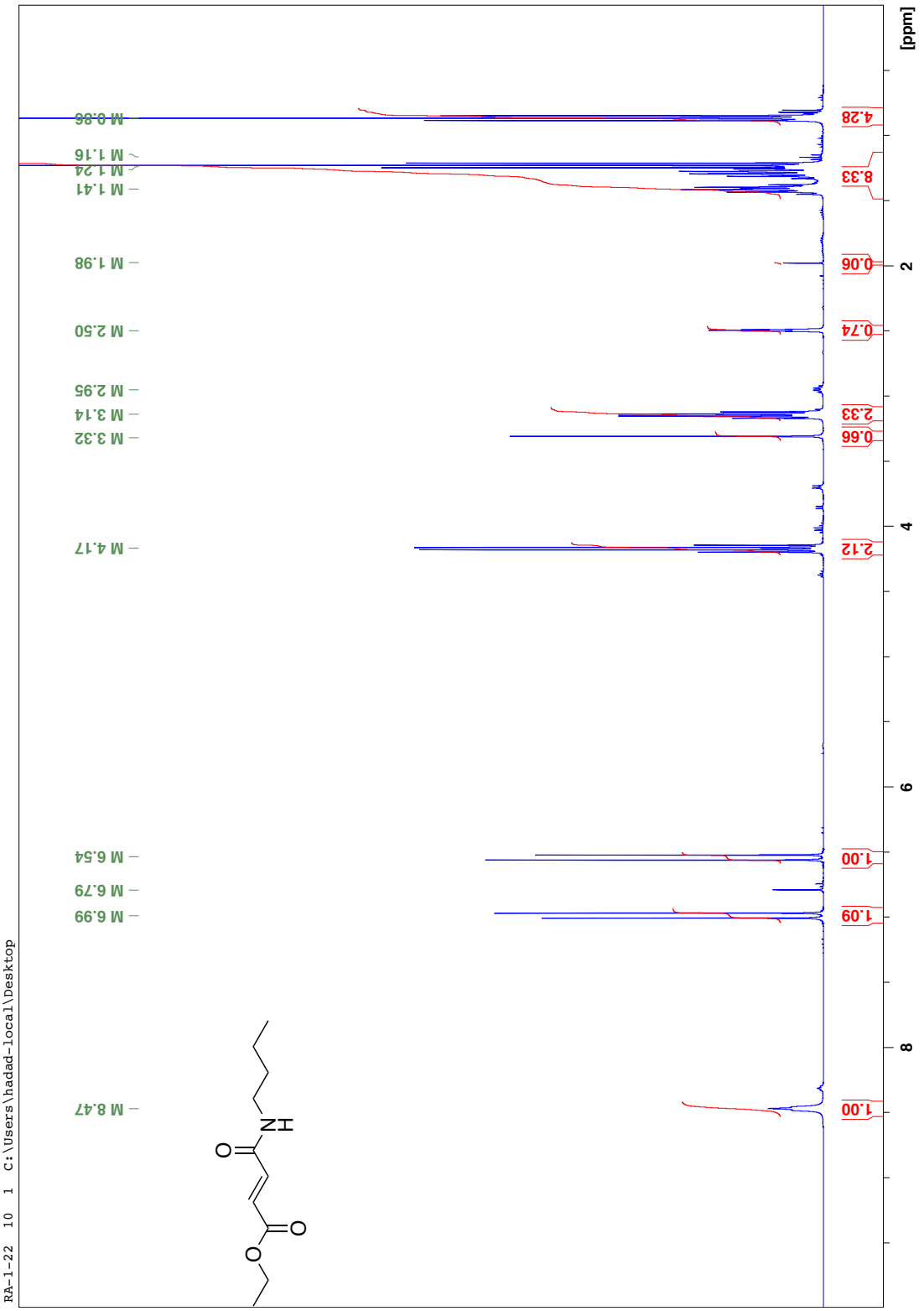
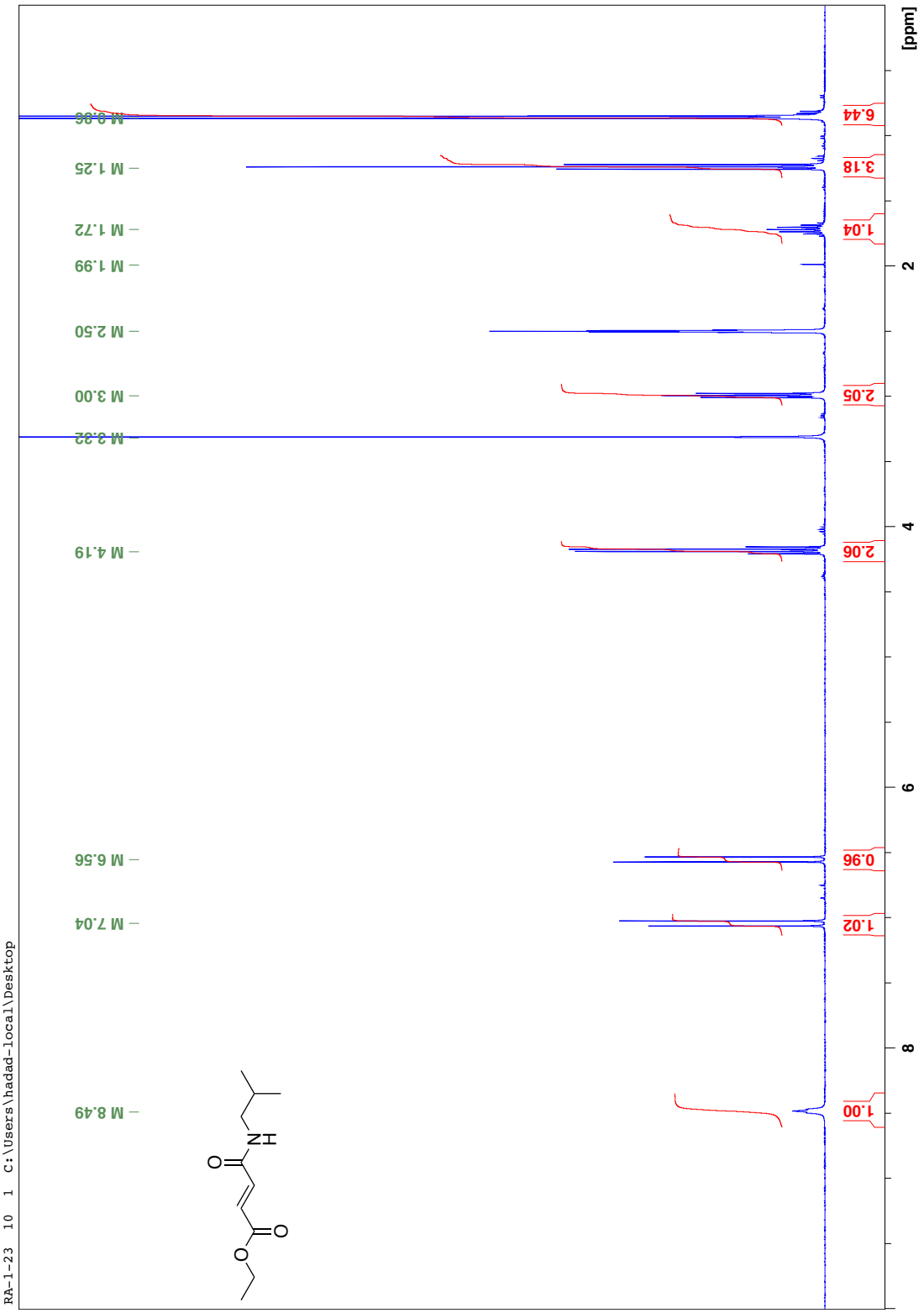
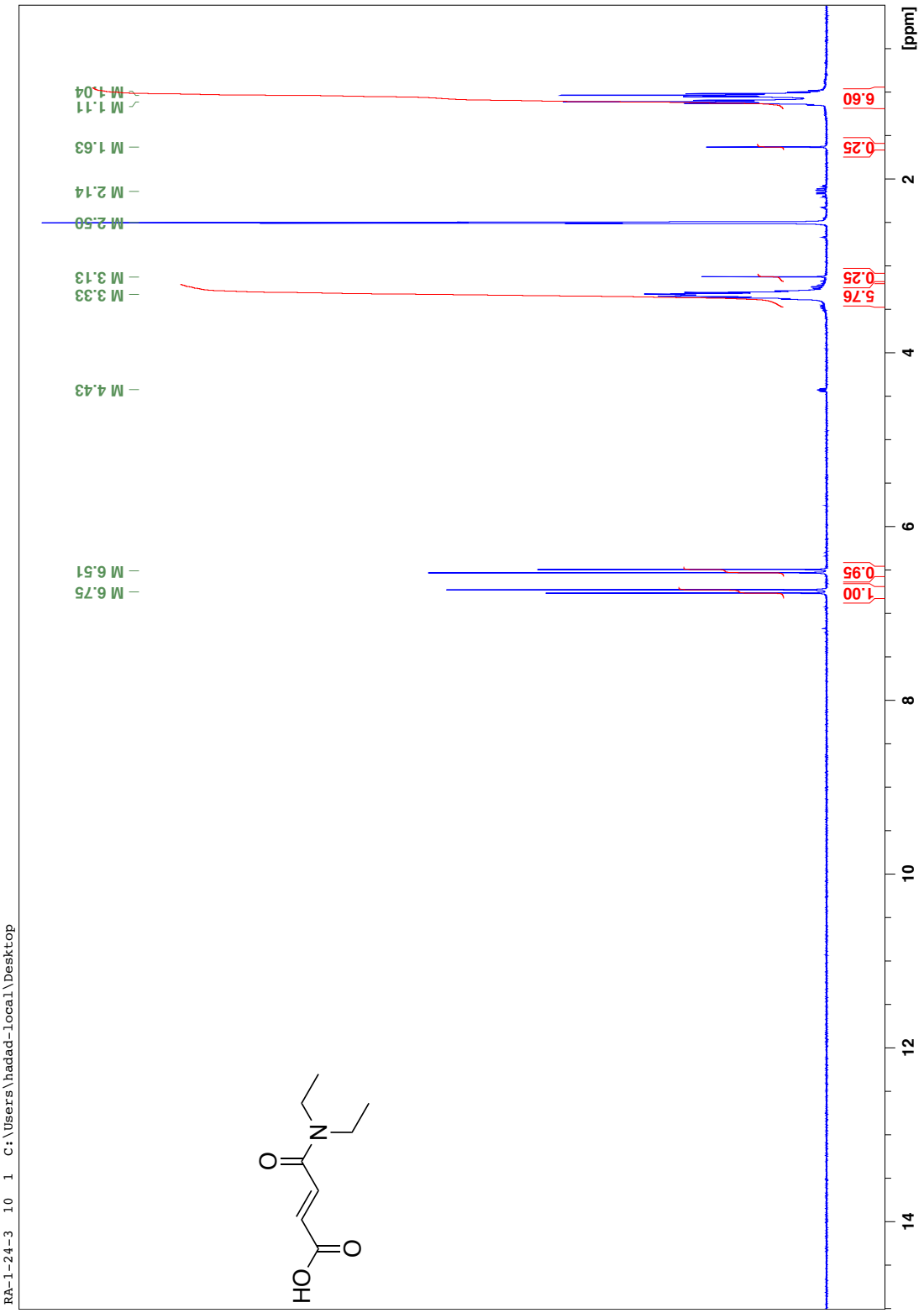
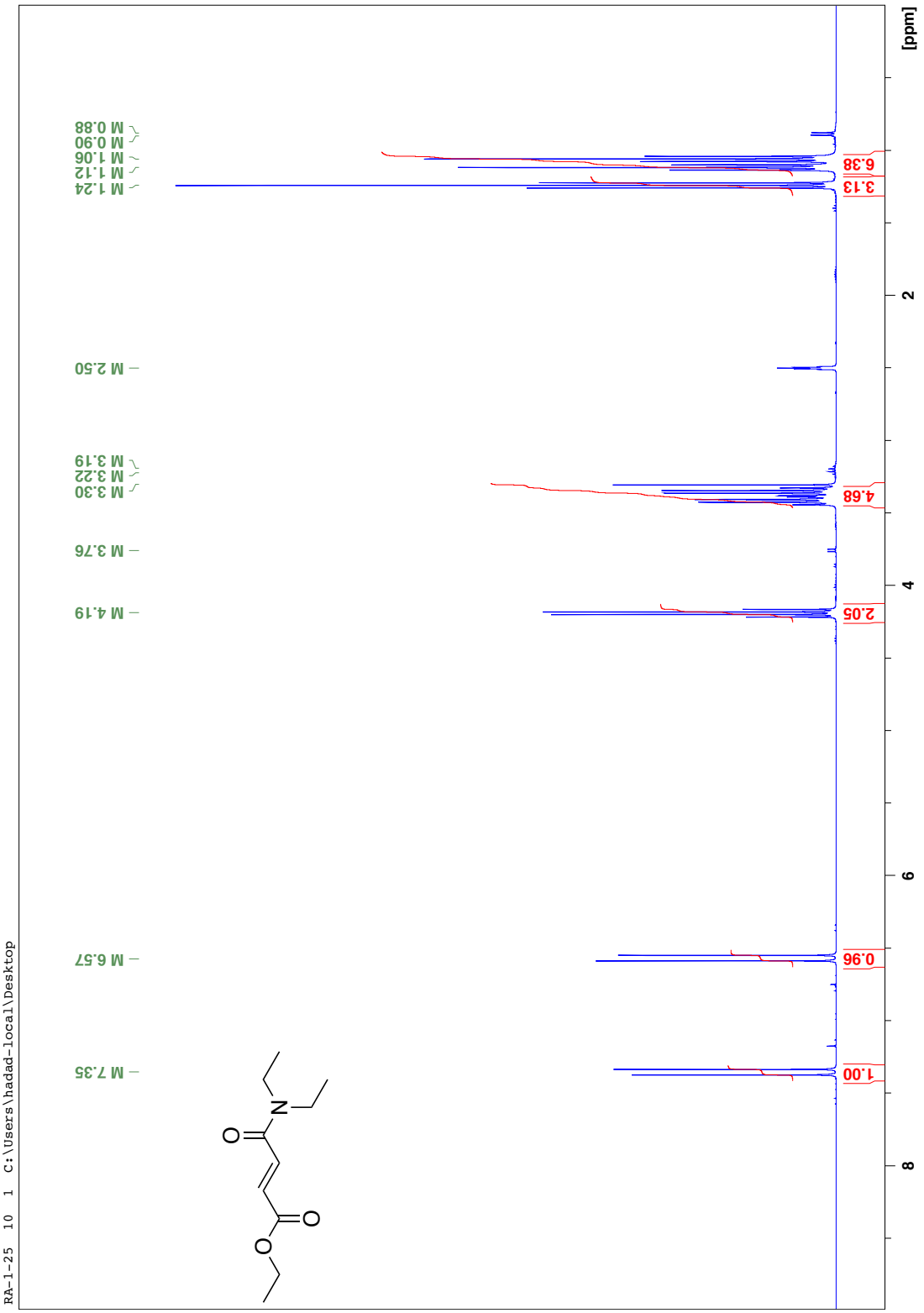
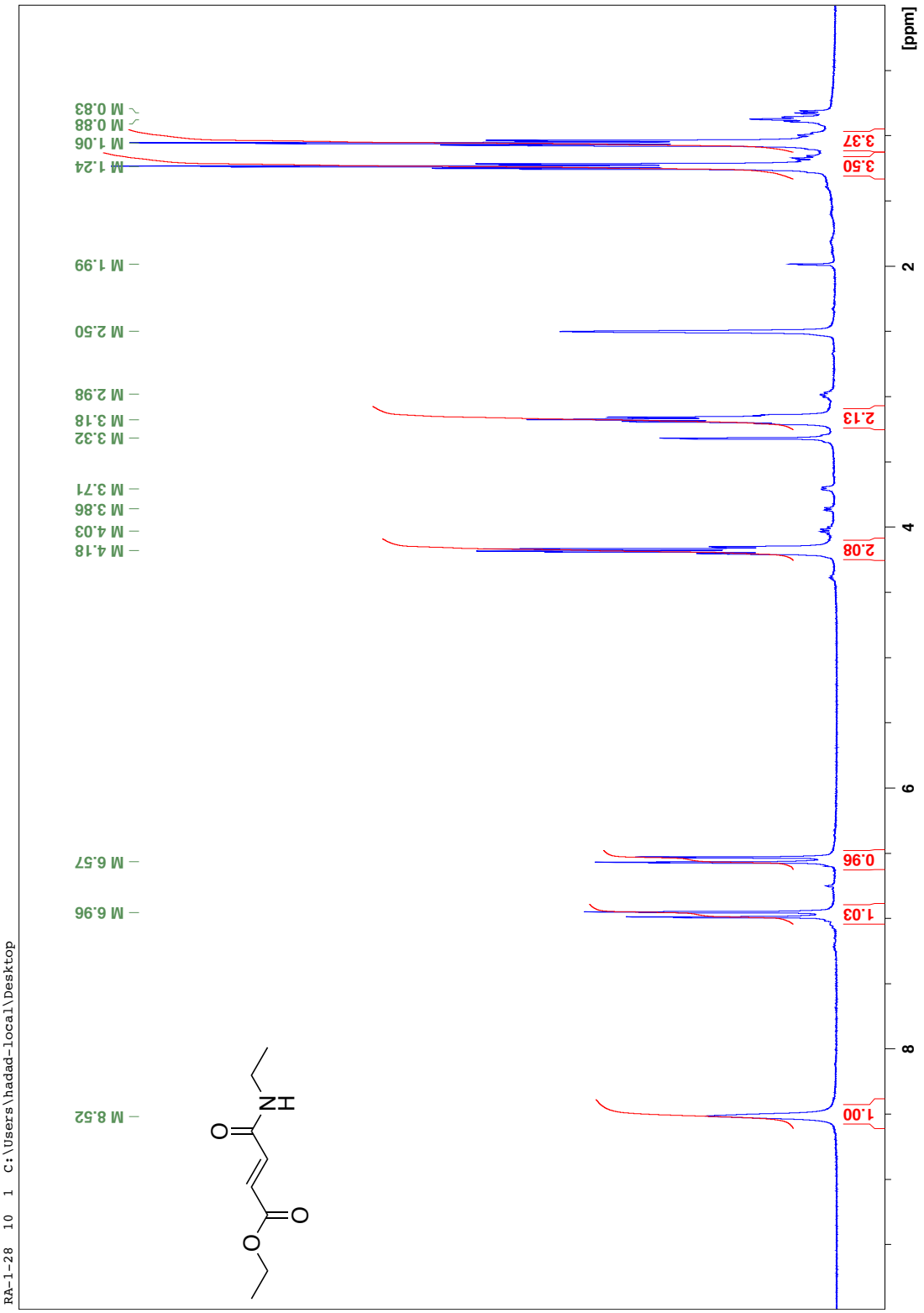
4
6
8
10
12
14
N
O
O
HO

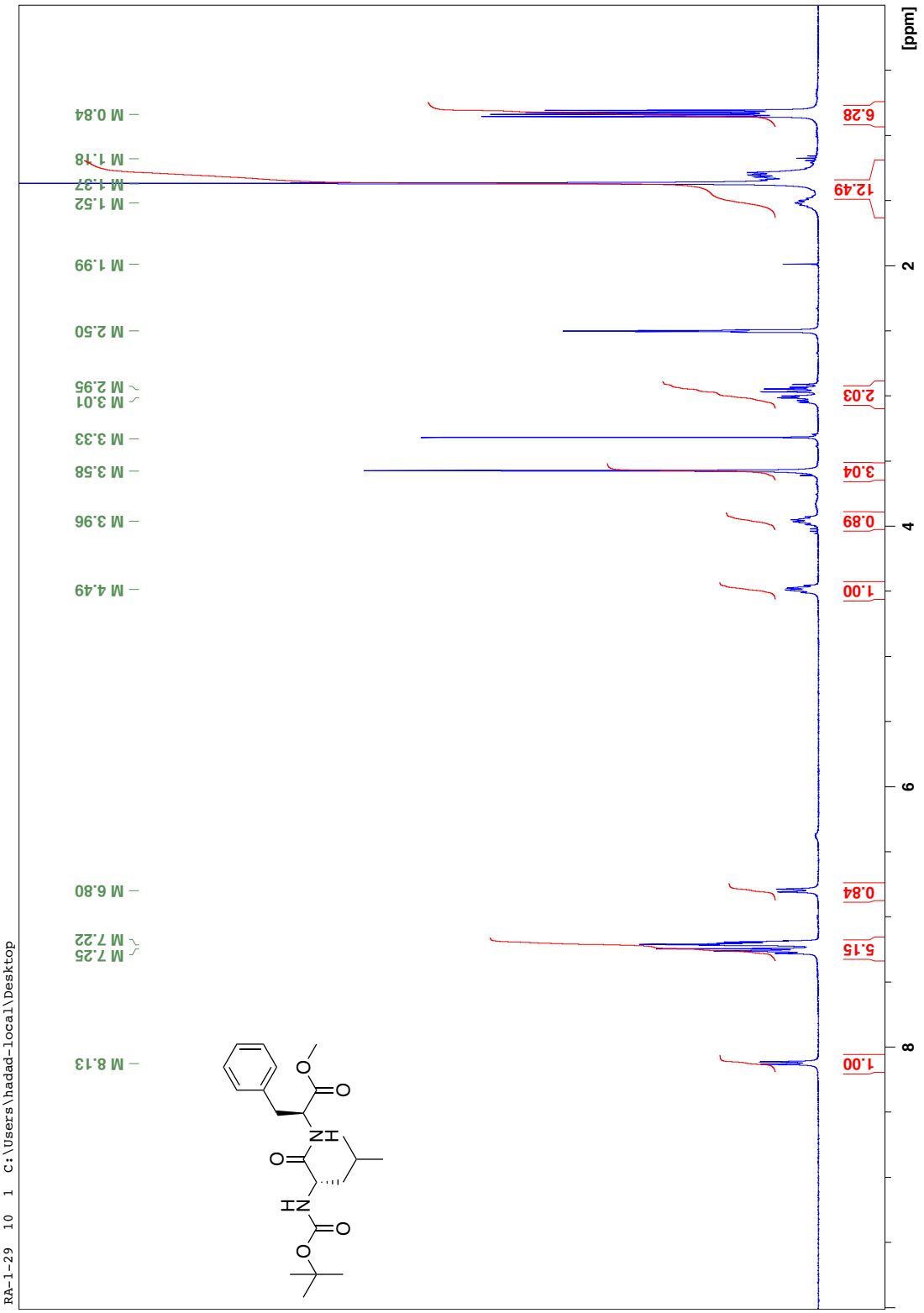

RA-1-22 10 1 C:\Users\hadad-local\Desktop
M 8.47
M 6.99
M 6.79
M 6.54
M 4.17
M 3.32
M 3.14
M 2.95
M 2.50
M 1.98
M 1.41
M 1.24
M 1.16
M 0.86
1.00
1.09
1.00
2.12
0.66
2.33
0.74
0.06
8.33
4.28
[ppm]
2
4
6
8
O
O
O
N
H

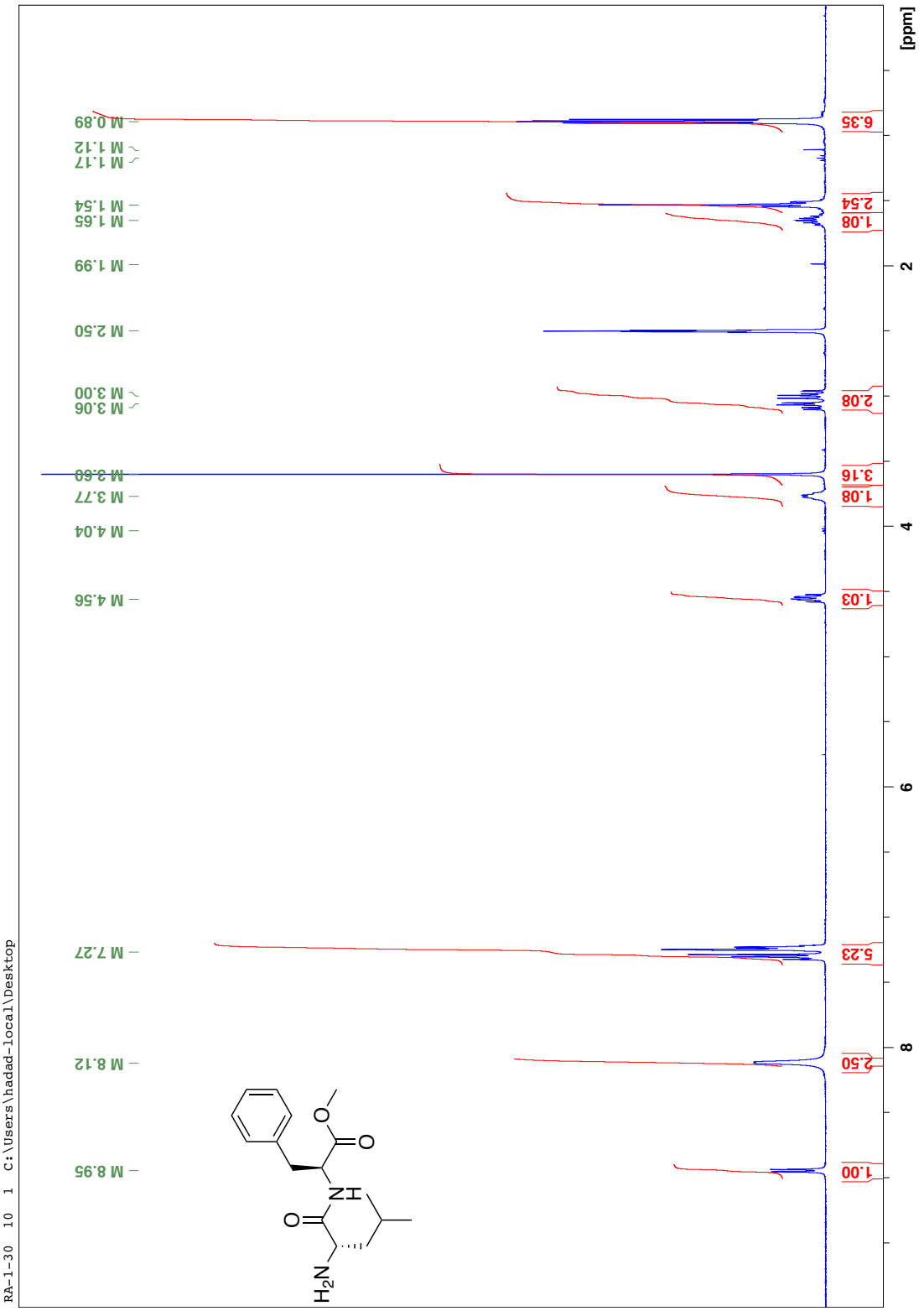

RA-1-23 10 1 C:\Users\hadad-local\Desktop
M 8.49
M 7.04
M 6.56
M 4.19
M 3.32
M 3.00
M 2.50
M 1.99
M 1.72
M 1.25
M 0.86
1.00
1.02
0.96
2.06
2.05
1.04
3.18
6.44
[ppm]
2
4
6
8
HN
O
O
O

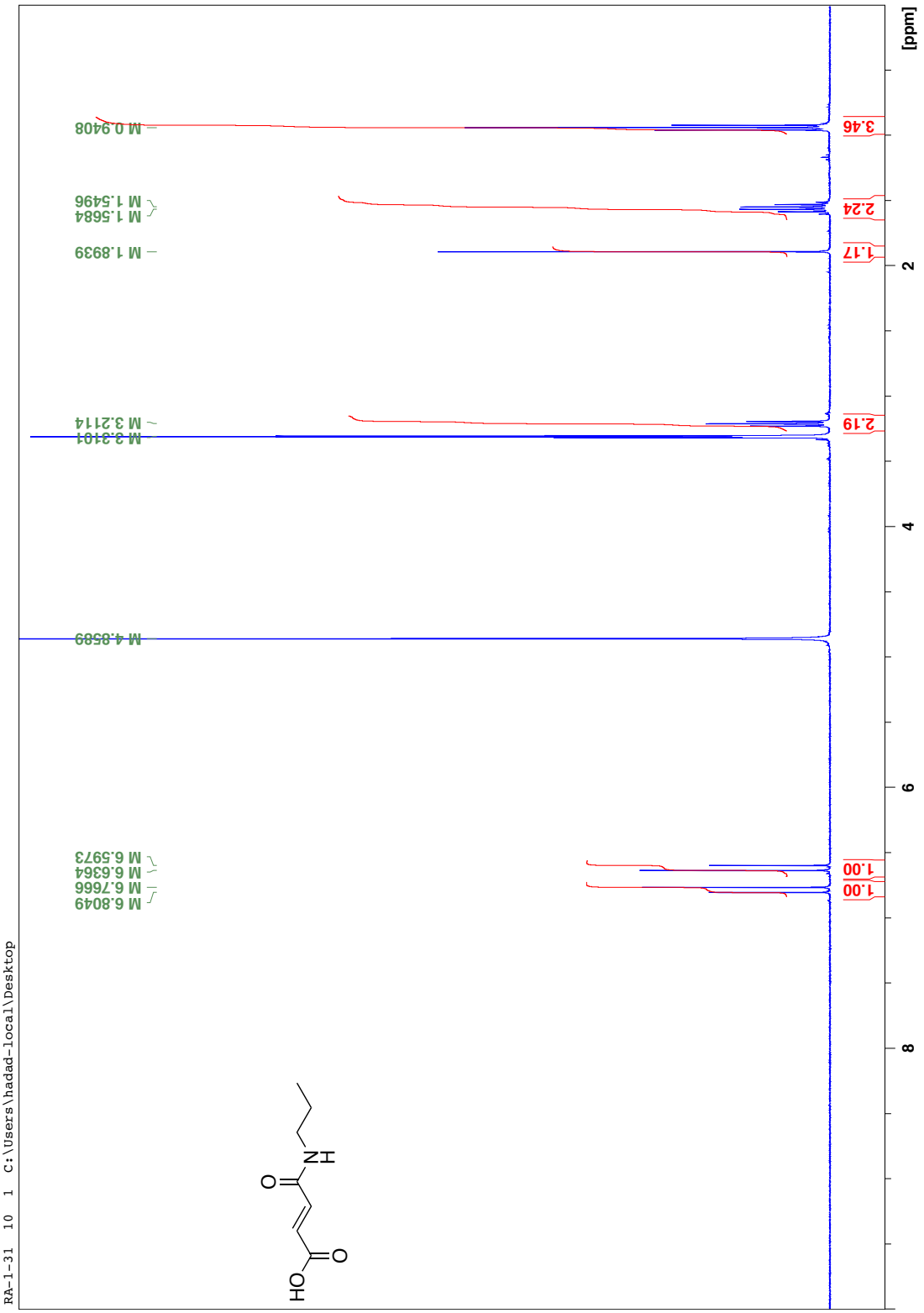

RA-1-24-3 10 1 C:\Users\hadad-local\Desktop
M 1.04
M 1.11
M 1.63
M 2.14
M 2.50
M 3.13
M 3.33
M 4.43
M 6.51
M 6.75
6.60
0.25
0.25
5.76
0.95
1.00
[ppm]
2
4
6
8
10
12
14
N
O
O
HO

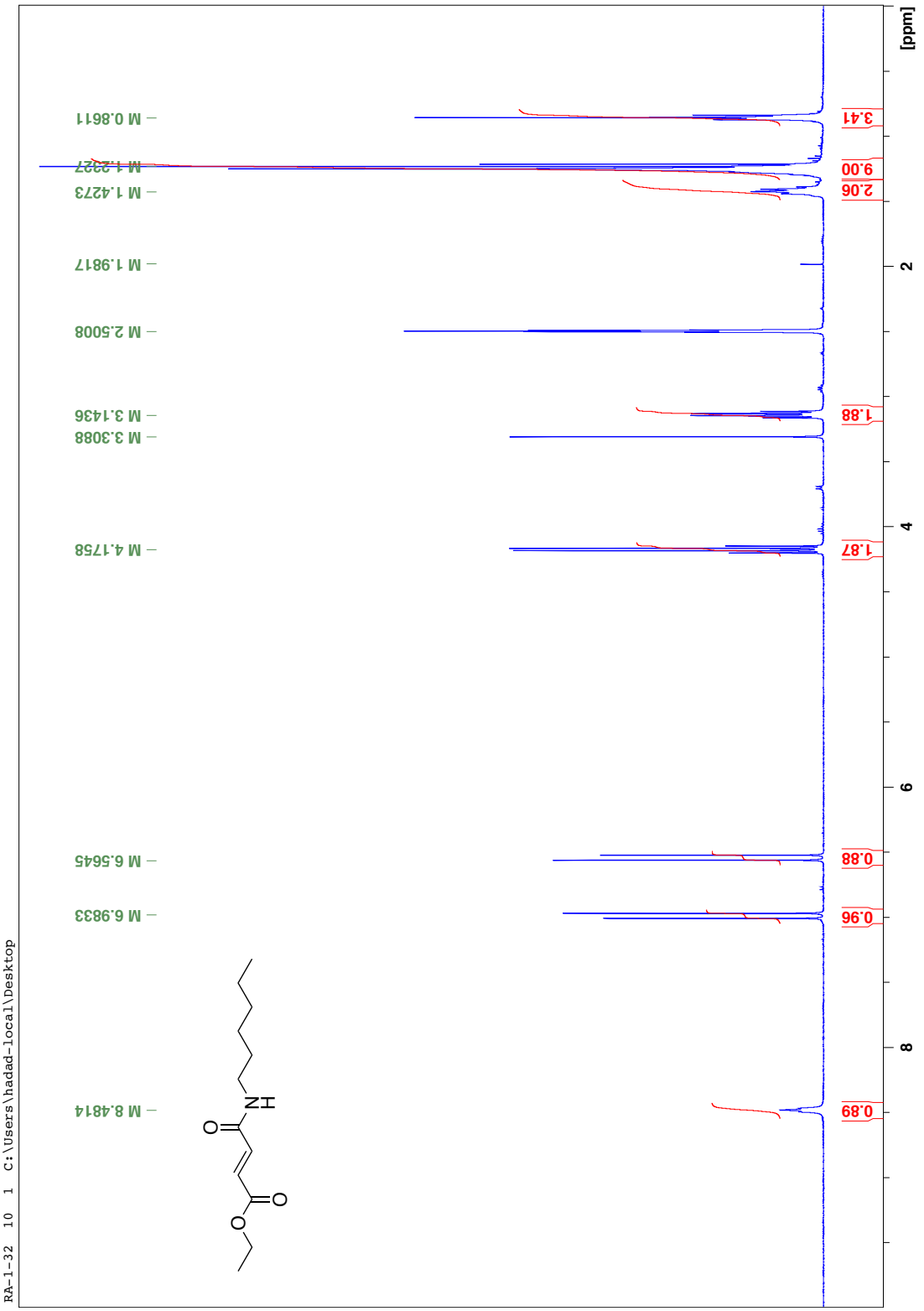

RA-1-25 10 1 C:\Users\hadad-local\Desktop
M 7.35
M 6.57
M 4.19
M 3.76
M 3.30
M 3.22
M 3.19
M 2.50
M 1.24
M 1.12
M 1.06
M 0.90
M 0.88
1.00
0.96
2.05
4.68
3.13
6.38
8
6
4
2
[ppm]
O
N
O
O
O

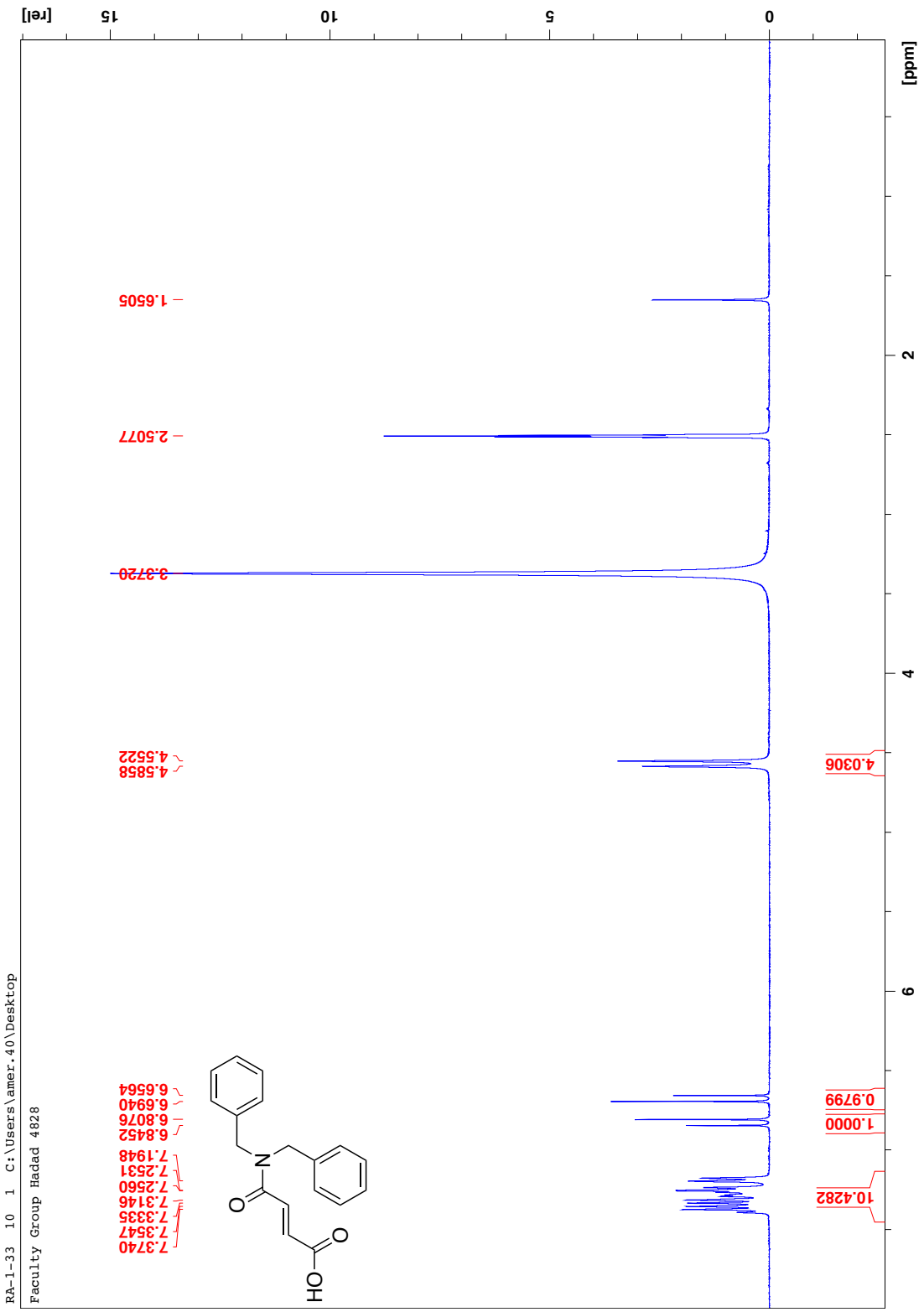

RA-1-28 10 1 C:\Users\hadad-local\Desktop
M 8.52
M 6.96
M 6.57
M 4.18
M 4.03
M 3.86
M 3.71
M 3.32
M 3.18
M 2.98
M 2.50
M 1.99
M 1.24
M 1.06
M 0.88
M 0.83
1.00
1.03
0.96
2.08
2.13
3.50
3.37
[ppm]
2
4
6
8
O
N
H
O
O


RA-1-29 10 1 C:\Users\hadad-local\Desktop
M 0.84
M 1.18
M 1.37
M 1.52
M 1.99
M 2.50
M 2.95
M 3.01
M 3.33
M 3.58
M 3.96
M 4.49
M 6.80
M 7.22
M 7.25
M 8.13
6.28
12.49
2.03
3.04
0.89
1.00
0.84
5.15
1.00
[ppm]
2
4
6
8
O
O
NH
O
NH
O
O


RA-1-30 10 1 C:\Users\hadad-local\Desktop
M 0.89
M 1.12
M 1.17
M 1.54
M 1.65
M 1.99
M 2.50
M 3.00
M 3.06
M 3.60
M 3.77
M 4.04
M 4.56
M 7.27
M 8.12
M 8.95
6.35
2.54
1.08
2.08
3.16
1.08
1.03
5.23
2.50
1.00
[ppm]
2
4
6
8
O
O
N
H
O
H2N


RA-1-31 10 1 C:\Users\hadad-local\Desktop
M 6.8049
M 6.7666
M 6.6364
M 6.5973
M 4.8589
M 3.3101
M 3.2114
M 1.8939
M 1.5684
M 1.5496
M 0.9408
1.00
1.00
2.19
1.17
2.24
3.46
[ppm]
8
6
4
2
HO
O
O
N
H


RA-1-32 10 1 C:\Users\hadad-local\Desktop
M 8.4814
M 6.9833
M 6.5645
M 4.1758
M 3.3088
M 3.1436
M 2.5008
M 1.9817
M 1.4273
M 1.2227
M 0.8611
0.89
0.96
0.88
1.87
1.88
2.06
9.00
3.41
[ppm]
2
4
6
8
NH
O
O
O


RA-1-33 10 1 C:\Users\amer.40\Desktop
Faculty Group Hadad 4828
[rel]
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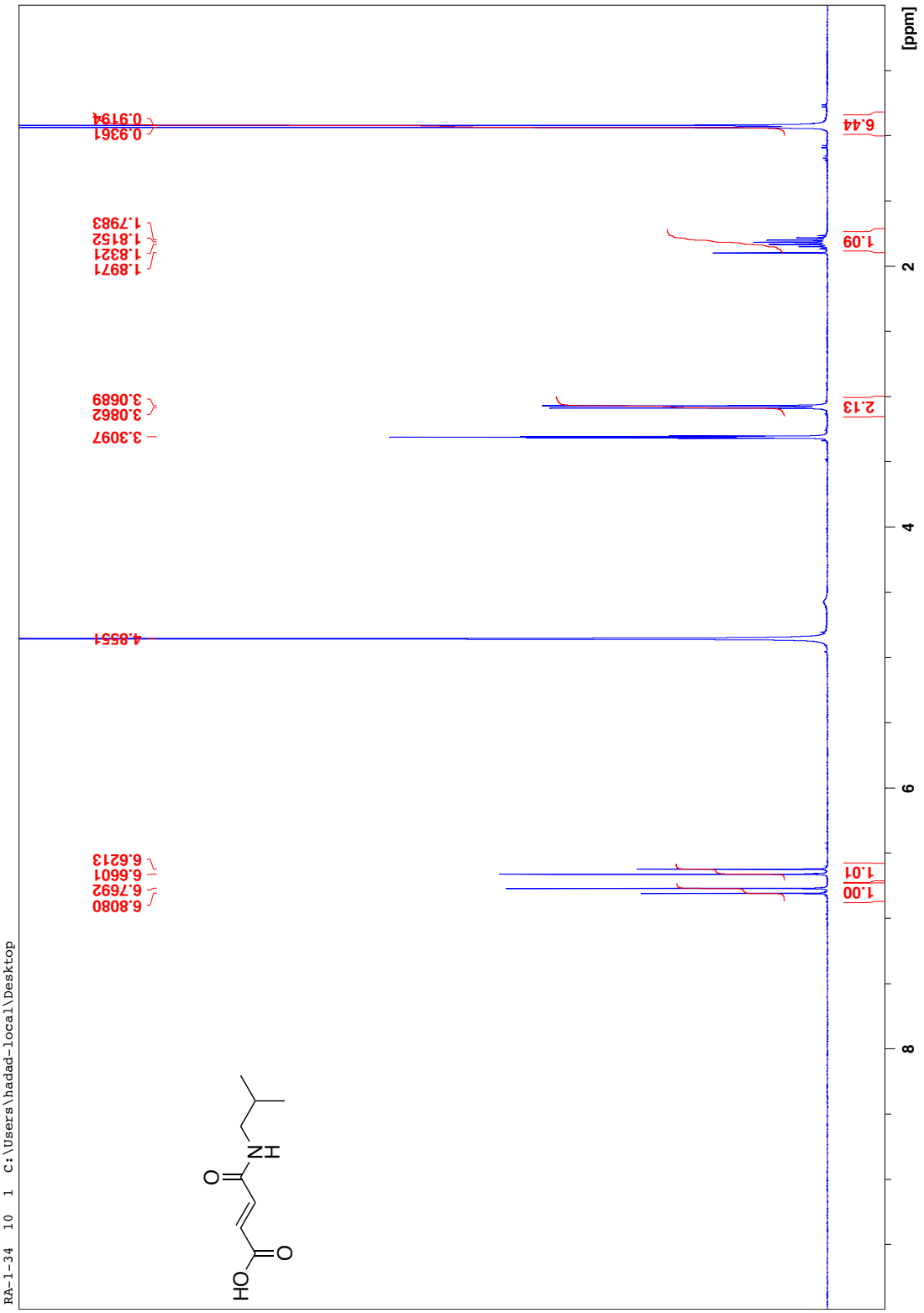
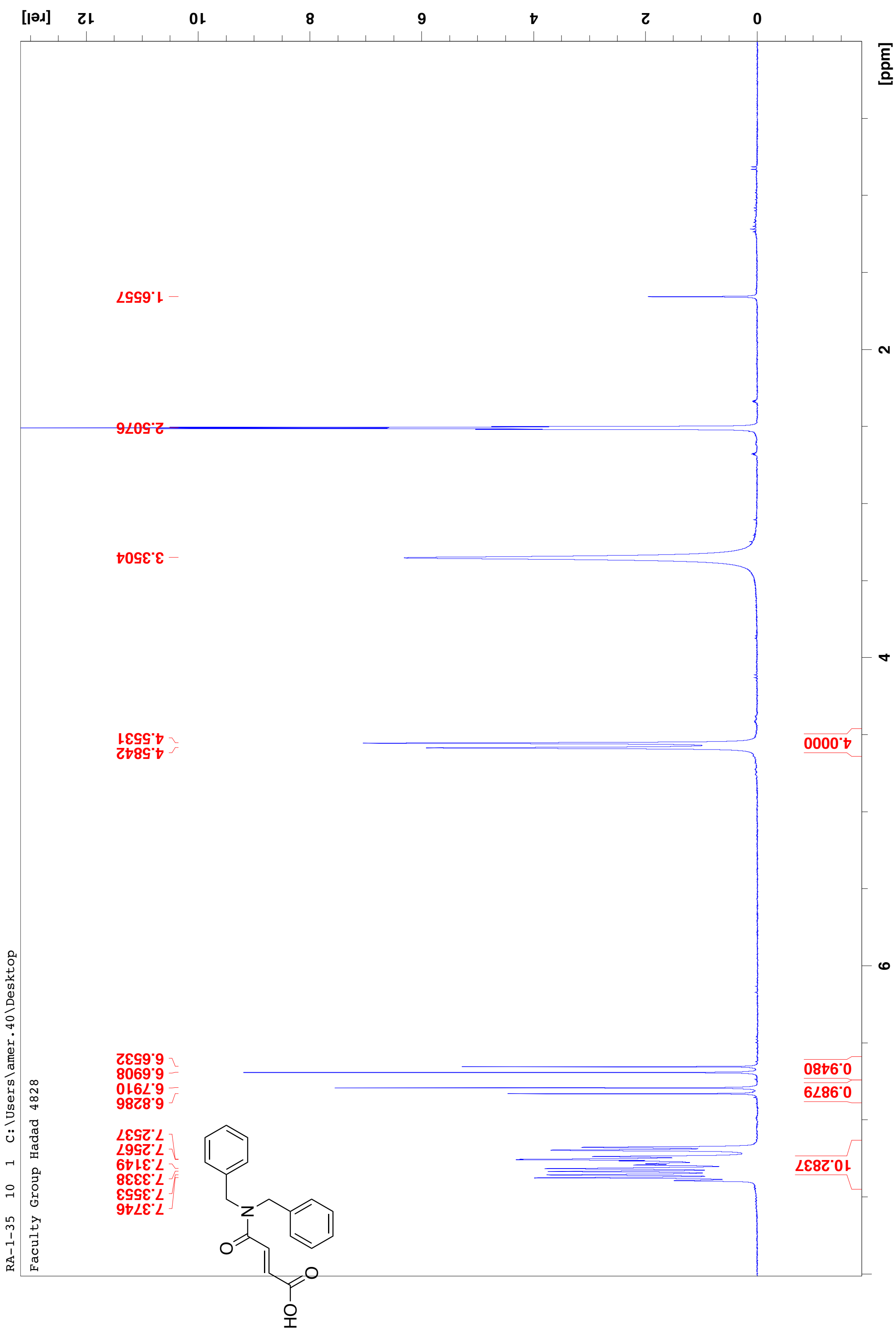
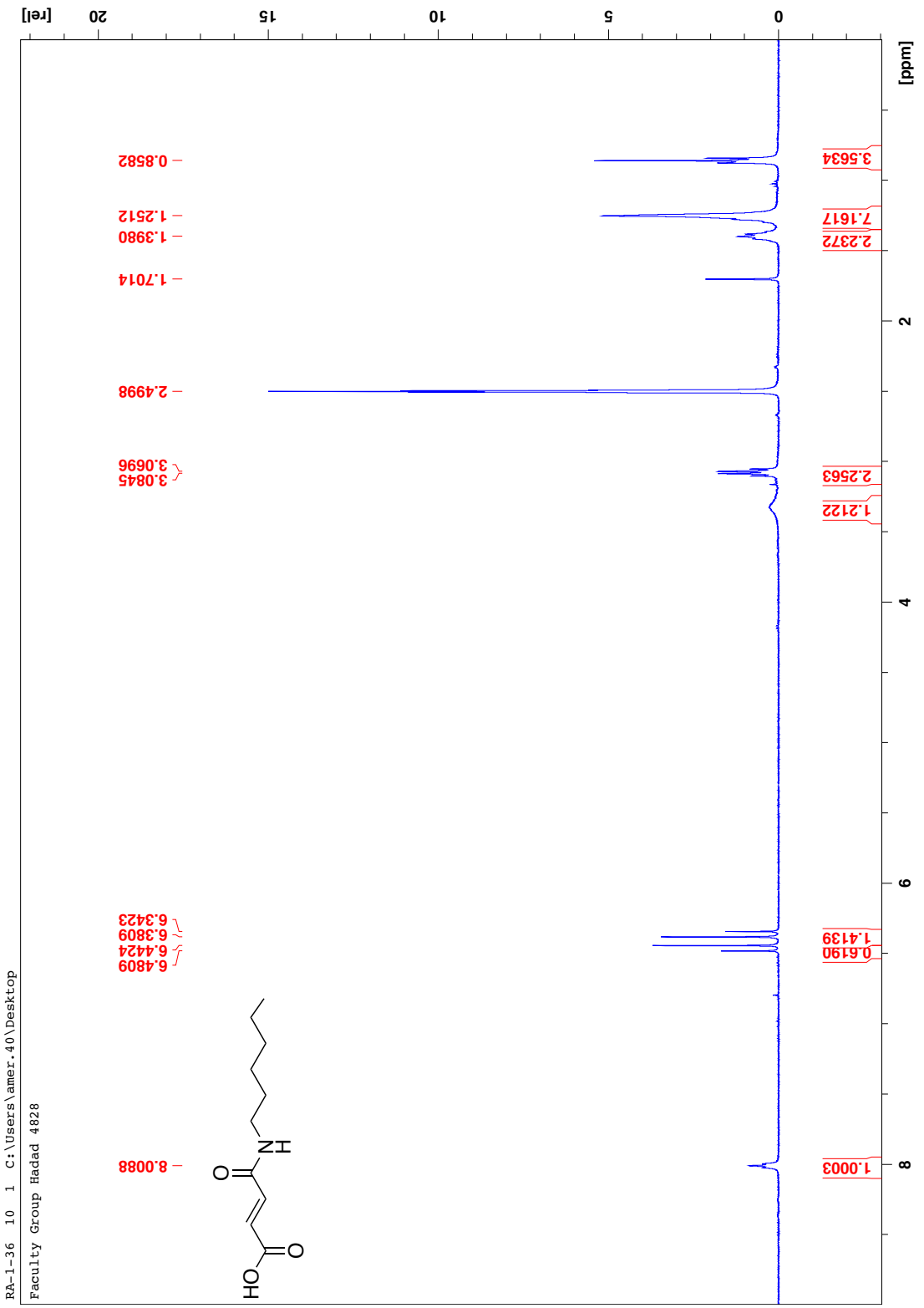
10
5
0
[ppm]
6
4
2
1.6505
2.5077
3.3720
4.5858
4.5522
6.6564
6.6940
6.8076
6.8452
7.1948
7.2531
7.2560
7.3146
7.3335
7.3547
7.3740
4.0306
10.4282
0.9799
1.0000
N
O
O
HO


RA-1-34 10 1 C:\Users\hadad-local\Desktop
6.8080
6.7692
6.6601
6.6213
4.8551
3.3097
3.0862
3.0689
1.8971
1.8321
1.8152
1.7983
0.9361
0.9194
1.00
1.01
2.13
1.09
6.44
[ppm]
2
4
6
8
HO
O
O
N
H


RA-1-35 10 1 C:\Users\amer.40\Desktop
Faculty Group Hadad 4828
7.3746
7.3553
7.3338
7.3149
7.2567
7.2537
6.8286
6.7910
6.6908
6.6532
4.5842
4.5531
3.3504
2.5076
1.6557
10.2837
0.9879
0.9480
4.0000
[ppm]
[rel]


RA-1-36 10 1 C:\Users\amer.40\Desktop
Faculty Group Hadad 4828
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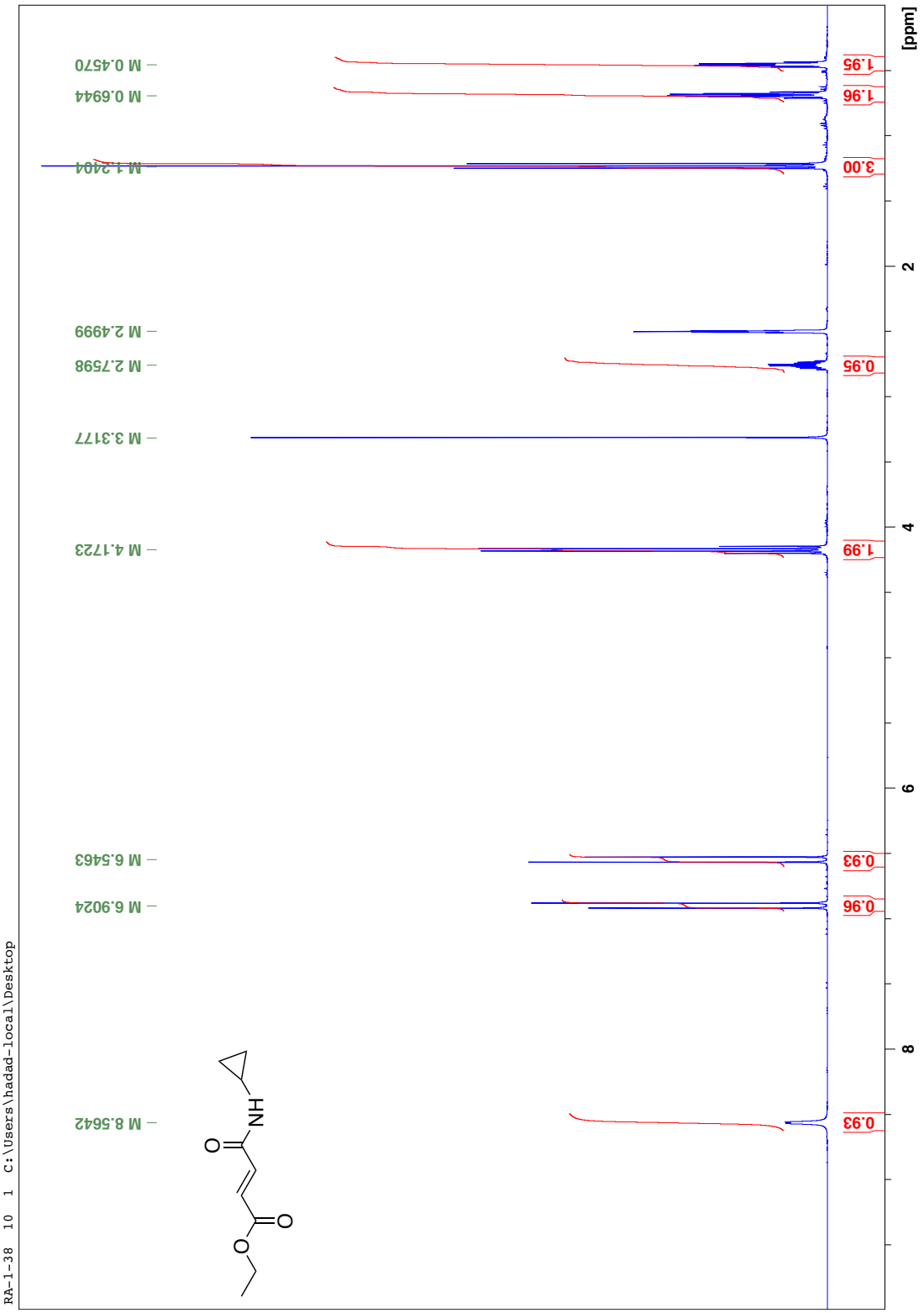
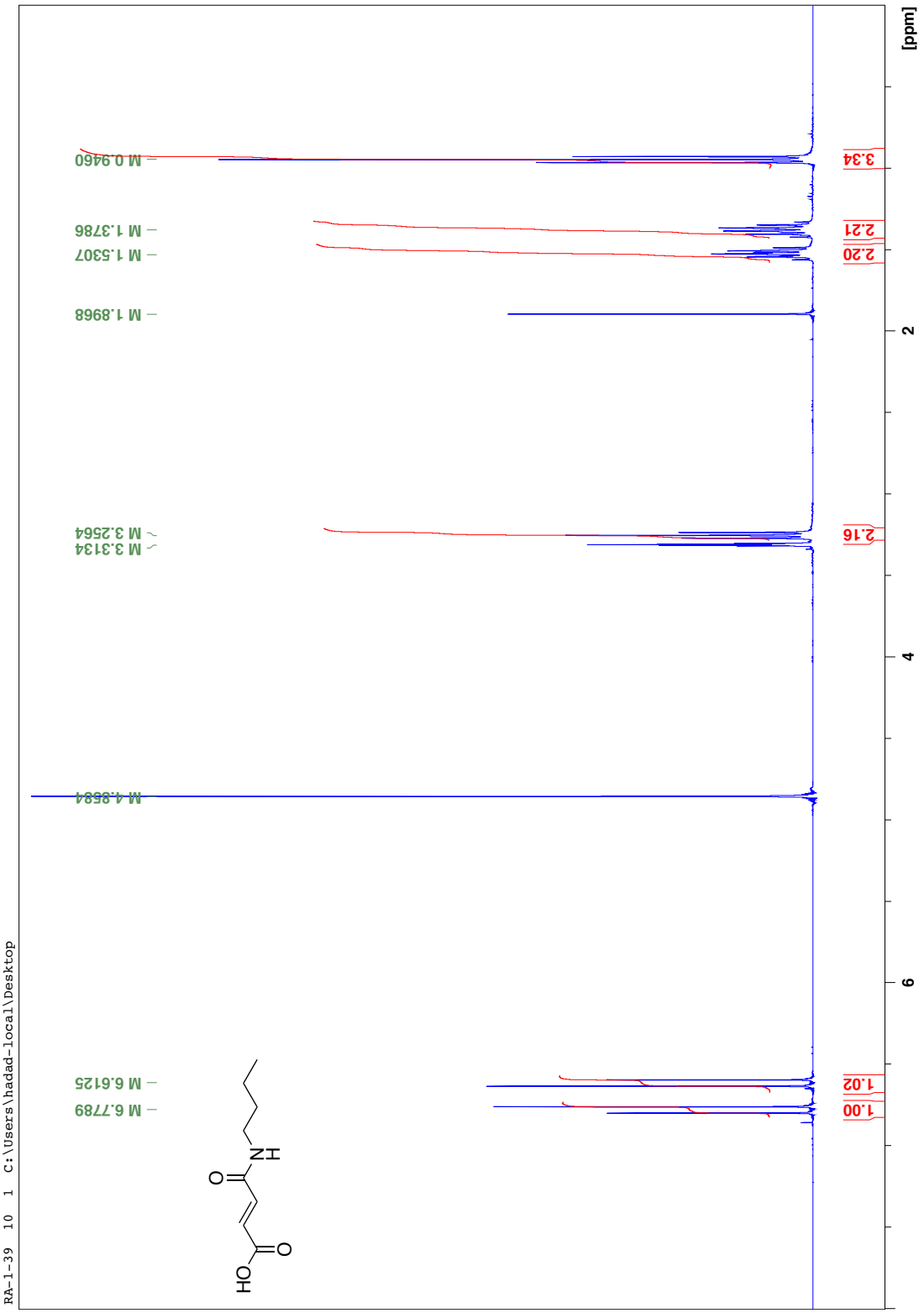
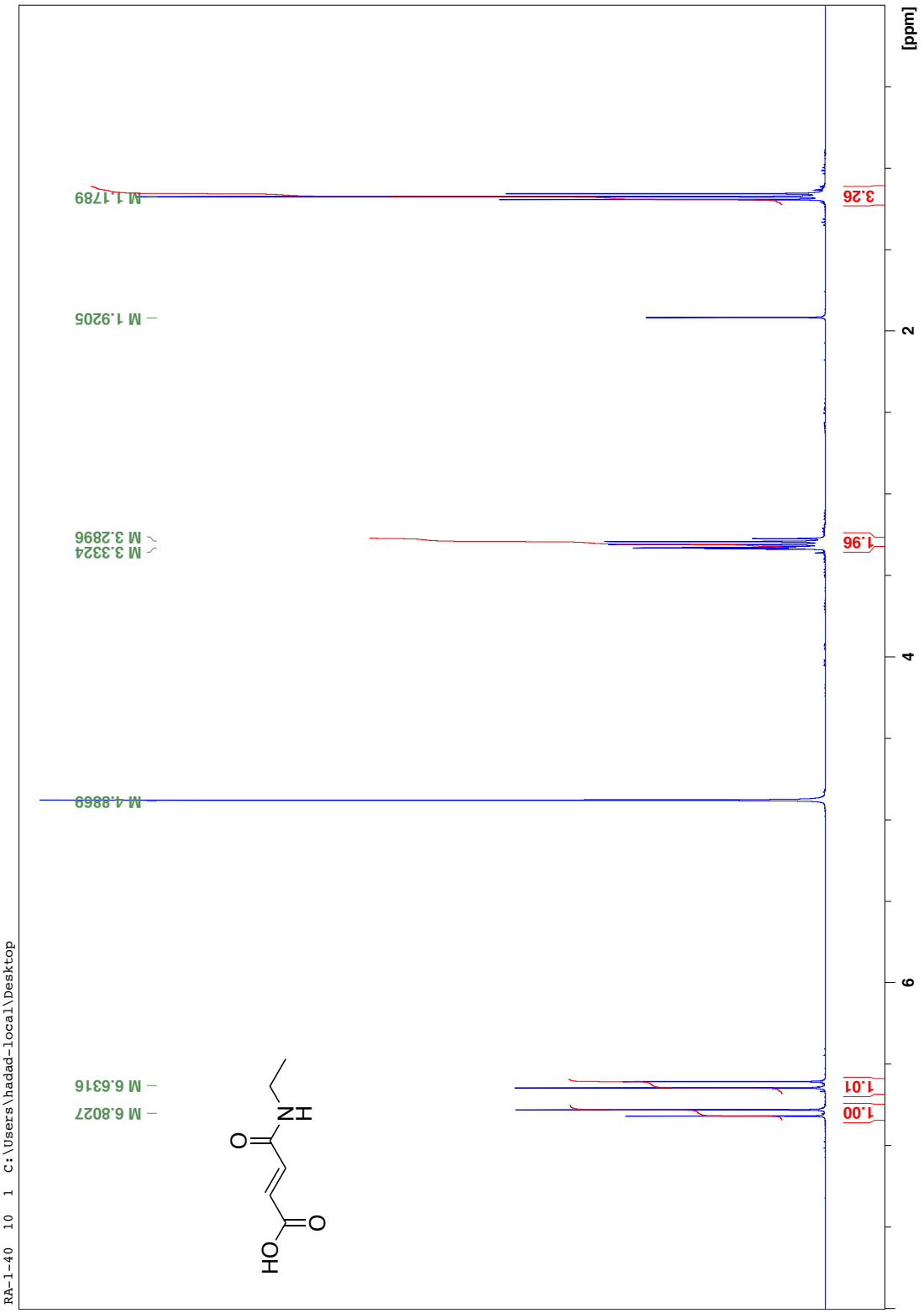
20
15
10
5
0
[ppm]
8
6
4
2
8.0088
6.4809
6.4424
6.3809
6.3423
3.0845
3.0696
2.4998
1.7014
1.3980
1.2512
0.8582
1.0003
0.6190
1.4139
3.5634
7.1617
2.2372
2.2563
1.2122
HO
O
O
NH


RA-1-38 10 1 C:\Users\hadad-local\Desktop
M 8.5642
M 6.9024
M 6.5463
M 4.1723
M 3.3177
M 2.7598
M 2.4999
M 1.2404
M 0.6944
M 0.4570
0.93
0.96
0.93
1.99
0.95
3.00
1.96
1.95
[ppm]
2
4
6
8
HN
O
O
O


RA-1-39 10 1 C:\Users\hadad-local\Desktop
M 6.7789
M 6.6125
M 4.8584
M 3.3134
M 3.2564
M 1.8968
M 1.5307
M 1.3786
M 0.9460
1.00
1.02
2.16
2.20
2.21
3.34
[ppm]
6
4
2
HO
O
O
NH


RA-1-40 10 1 C:\Users\hadad-local\Desktop
M 6.8027
M 6.6316
M 4.8869
M 3.3324
M 3.2896
M 1.9205
M 1.1789
1.00
1.01
1.96
3.26
6
4
2
[ppm]
HO
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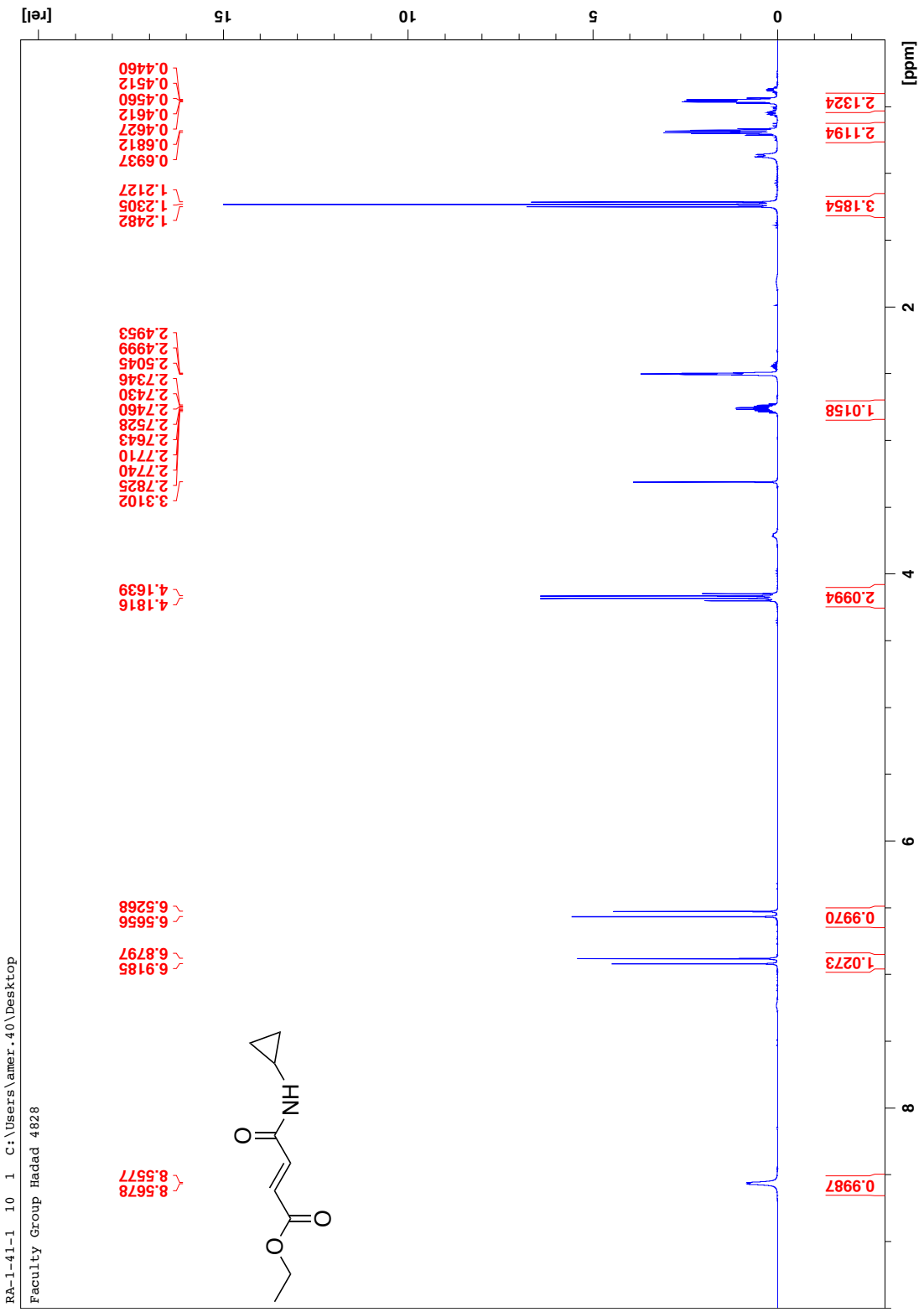
O
N
H


RA-1-41-1 10 1 C:\Users\amer.40\Desktop
Faculty Group Hadad 4828
[rel]
15
10
5
0
[ppm]
8
6
4
2
8.5678
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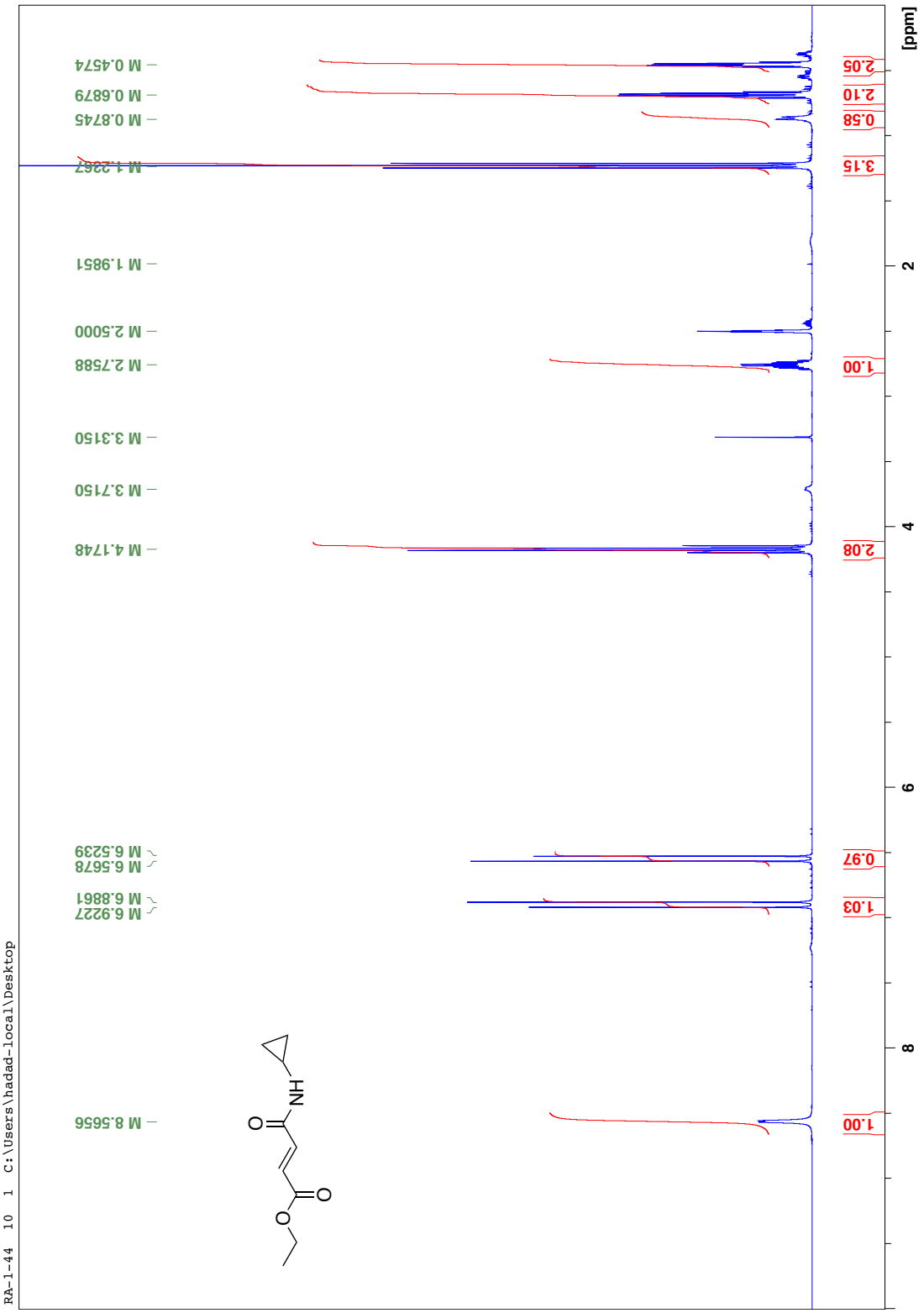
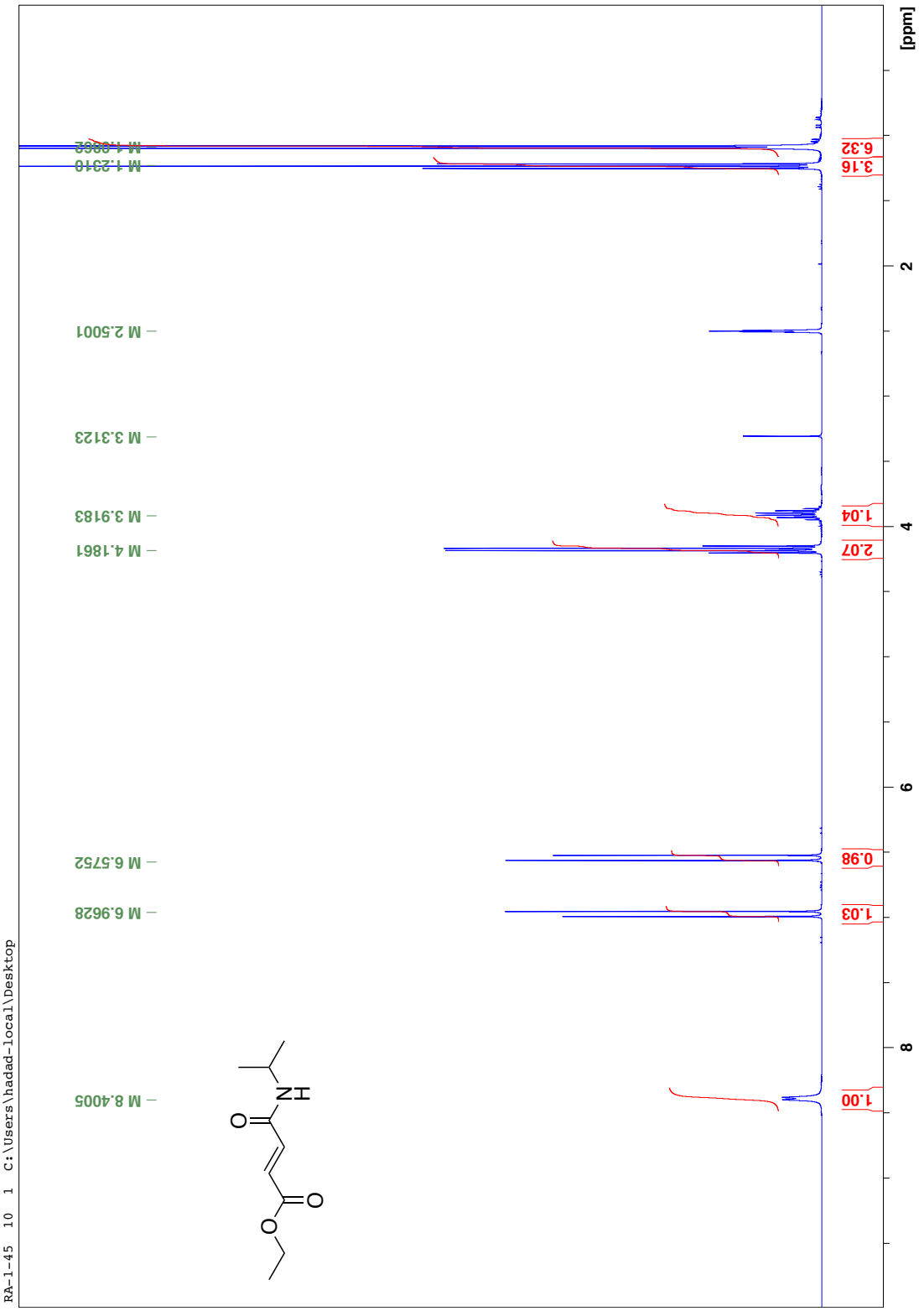
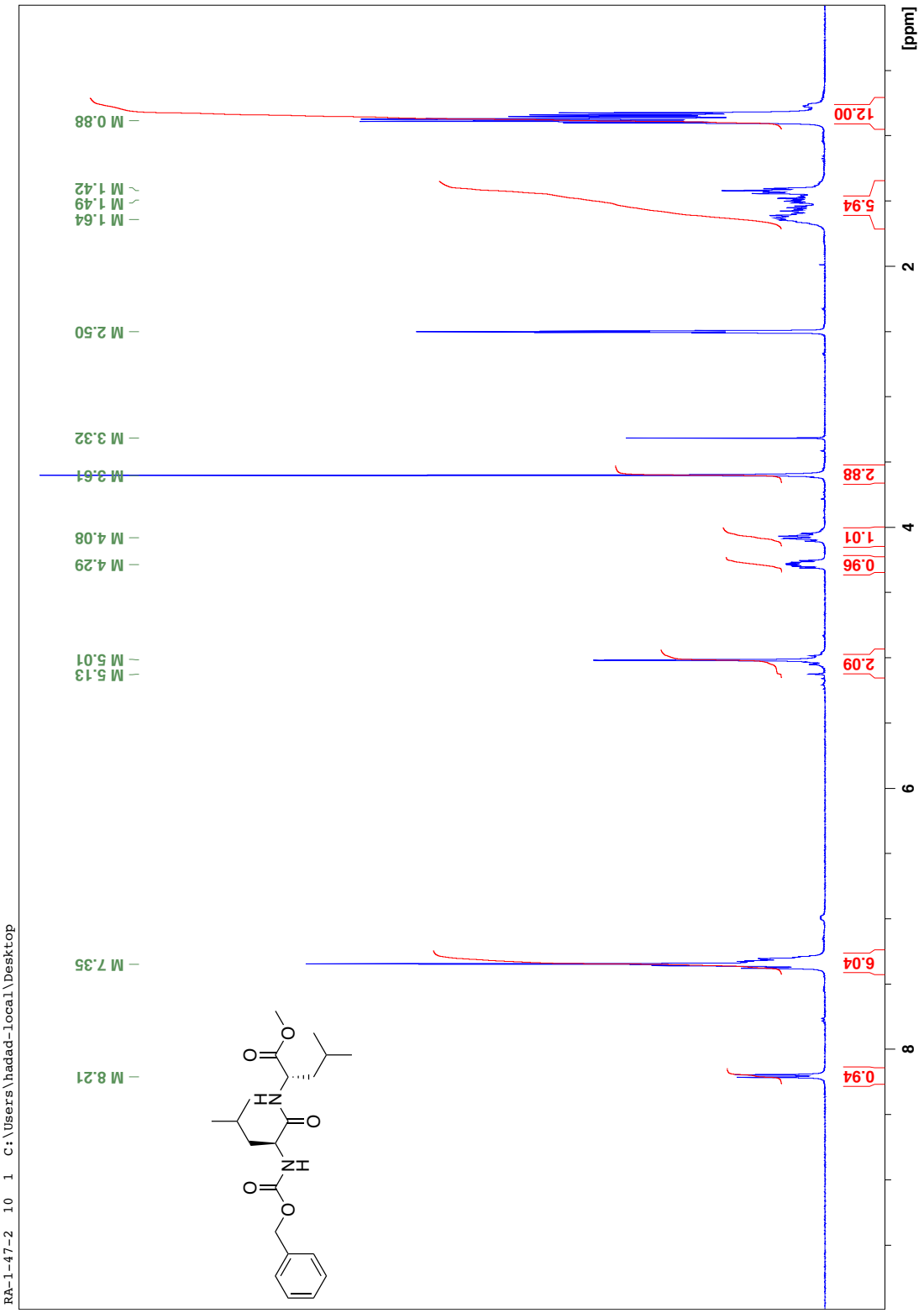
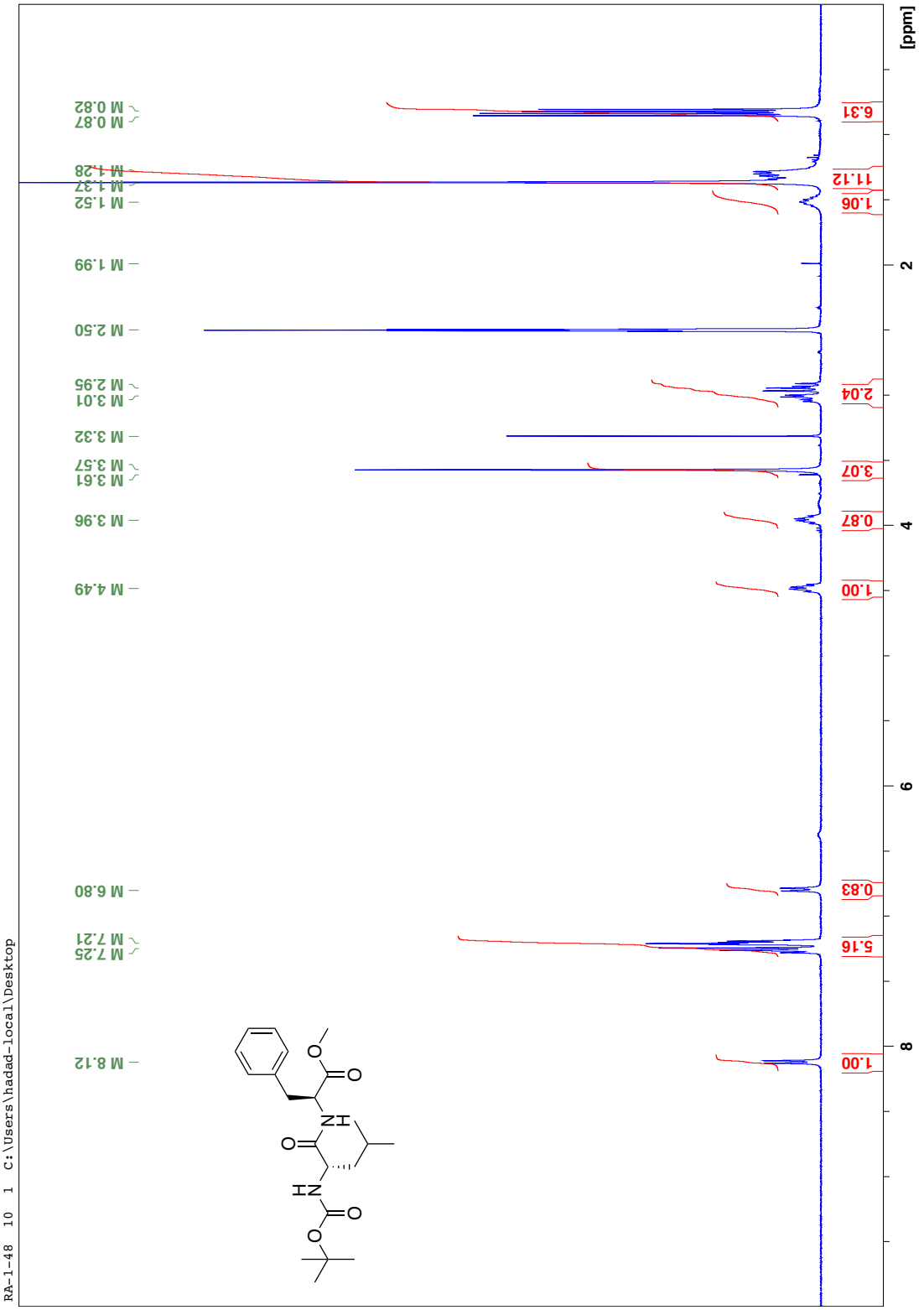
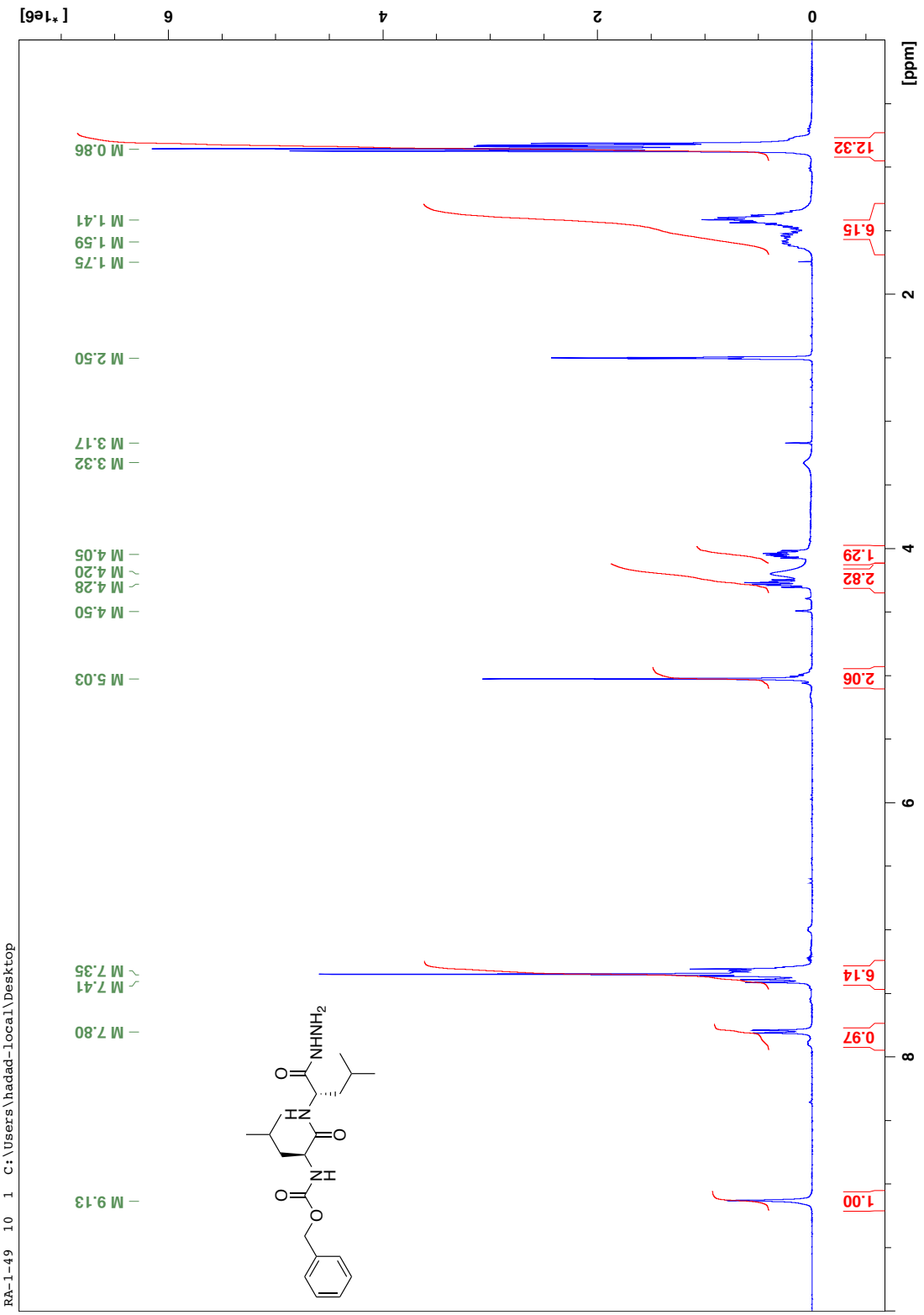
6.9185
6.8797
6.5656
6.5268
4.1816
4.1639
3.3102
2.7825
2.7740
2.7710
2.7643
2.7528
2.7460
2.7430
2.7346
2.5045
2.4999
2.4953
1.2482
1.2305
1.2127
0.6937
0.6812
0.4627
0.4612
0.4560
0.4512
0.4460
0.9987
1.0273
0.9970
2.0994
1.0158
3.1854
2.1194
2.1324
NH
O
O
O

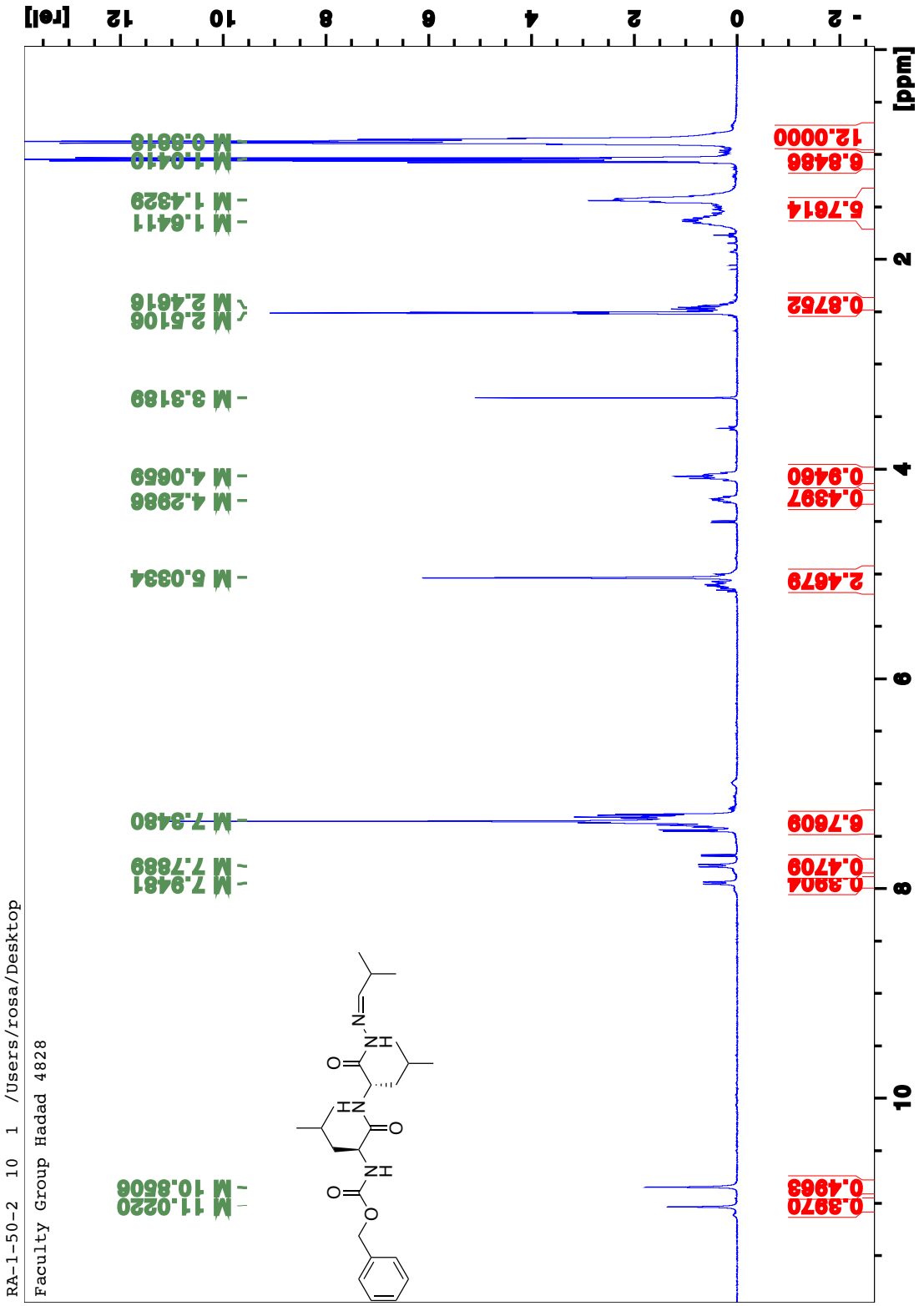

RA-1-44 10 1 C:\Users\hadad-local\Desktop
M 8.5656
M 6.9227
M 6.8861
M 6.5678
M 6.5239
M 4.1748
M 3.7150
M 3.3150
M 2.7588
M 2.5000
M 1.9851
M 1.2367
M 0.8745
M 0.6879
M 0.4574
1.00
1.03
0.97
2.08
1.00
3.15
0.58
2.10
2.05
[ppm]
2
4
6
8
NH
O
O
O


RA-1-45 10 1 C:\Users\hadad-local\Desktop
M 8.4005
M 6.9628
M 6.5752
M 4.1861
M 3.9183
M 3.3123
M 2.5001
M 1.2310
M 1.0062
1.00
1.03
0.98
2.07
1.04
3.16
6.32
8
6
4
2
[ppm]
HN
O
O
O


RA-1-47-2 10 1 C:\Users\hadad-local\Desktop
M 0.88
M 1.42
M 1.49
M 1.64
M 2.50
M 3.32
M 3.61
M 4.08
M 4.29
M 5.01
M 5.13
M 7.35
M 8.21
12.00
5.94
2.88
1.01
0.96
2.09
6.04
0.94
[ppm]
2
4
6
8
O
O
NH
O
NH
O
O


RA-1-48 10 1 C:\Users\hadad-local\Desktop
M 8.12
M 7.25
M 7.21
M 6.80
M 4.49
M 3.96
M 3.61
M 3.57
M 3.32
M 3.01
M 2.95
M 2.50
M 1.99
M 1.52
M 1.37
M 1.28
M 0.87
M 0.82
6.31
11.12
1.06
2.04
3.07
0.87
1.00
0.83
5.16
1.00
[ppm]
2
4
6
8
O
O
NH
O
NH
O
O


RA-1-49 10 1 C:\Users\hadad-local\Desktop
[ppm]
[*1e6]
M 9.13
M 7.80
M 7.41
M 7.35
M 5.03
M 4.50
M 4.28
M 4.20
M 4.05
M 3.32
M 3.17
M 2.50
M 1.75
M 1.59
M 1.41
M 0.86
1.00
0.97
6.14
2.06
2.82
1.29
6.15
12.32
NHNH2
O
N
H
O
N
H
O
O


RA-1-50-2 10 1 /Users/rosa/Desktop
Faculty Group Hadad 4828
[ppm]
[rel]
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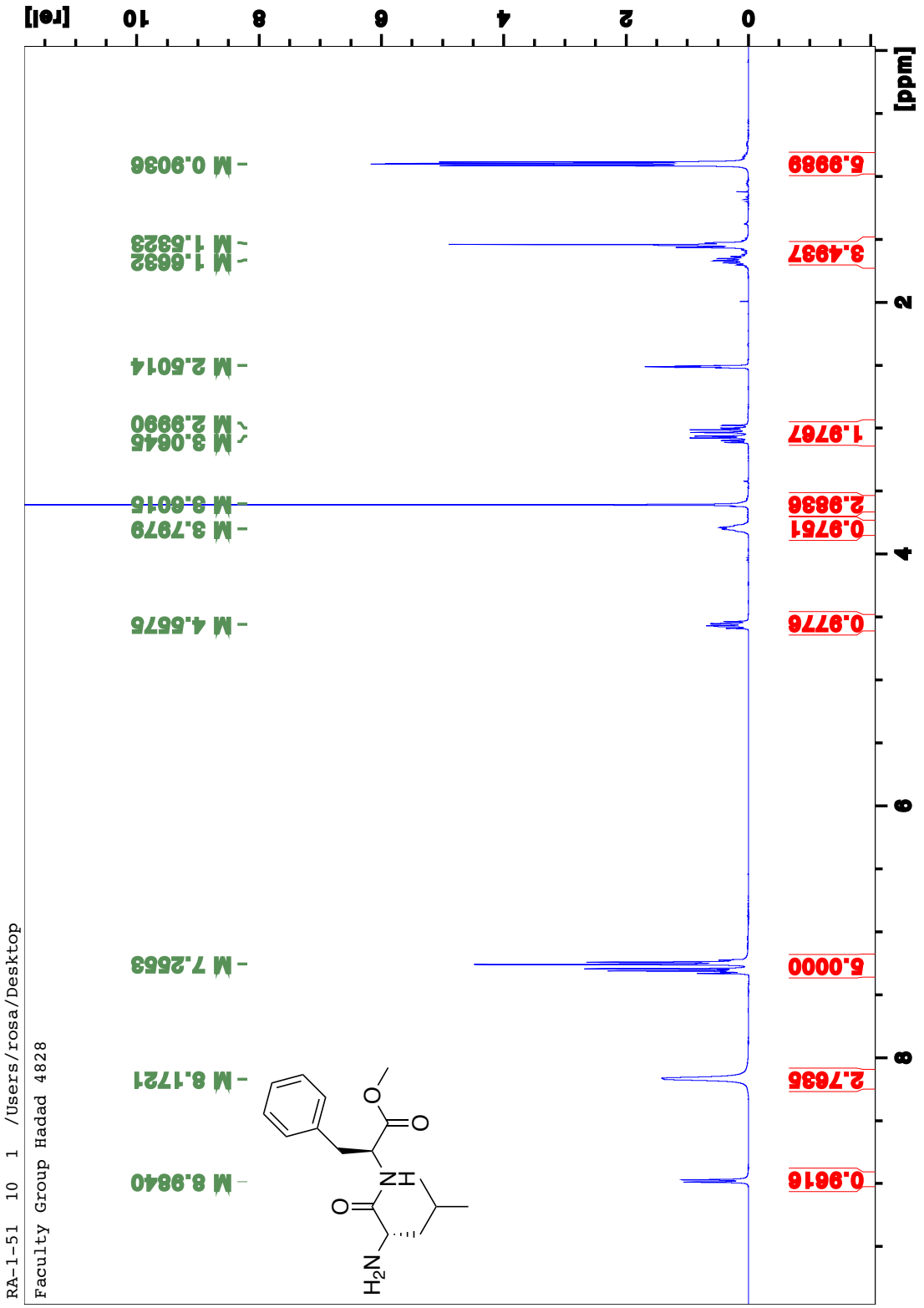
6.8486
6.7614
0.8762
2.4679
0.4397
0.9460
0.3904
0.4709
6.7609
0.4963
0.3970
M 0.3818
M 1.0410
M 1.4329
M 1.6411
M 2.4616
M 2.6106
M 3.3189
M 4.0659
M 4.2986
M 5.0334
M 7.3480
M 7.7889
M 7.9481
M 10.8506
M 11.0220


RA-1-51 10 1 /Users/rosa/Desktop
Faculty Group Hadad 4828
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4
6
8
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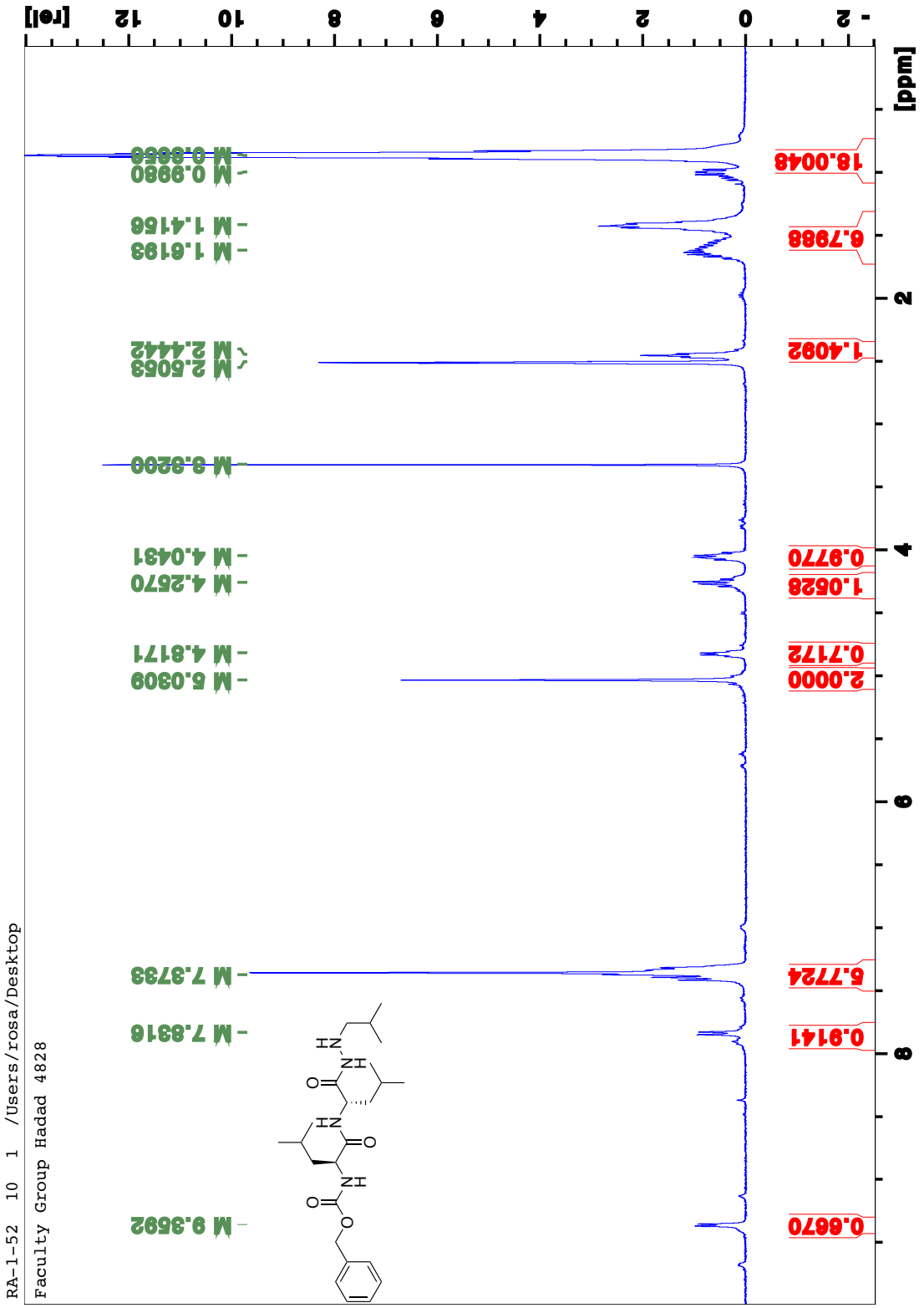
1.9767
2.9836
0.9761
0.9776
5.0000
2.7636
0.9616
M 0.9036
M 1.6632
M 1.6323
M 2.5014
M 2.9990
M 3.0645
M 3.6016
M 3.7979
M 4.5675
M 7.2653
M 8.1721
M 8.9840
O
O
NH
O
H2N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2.0000
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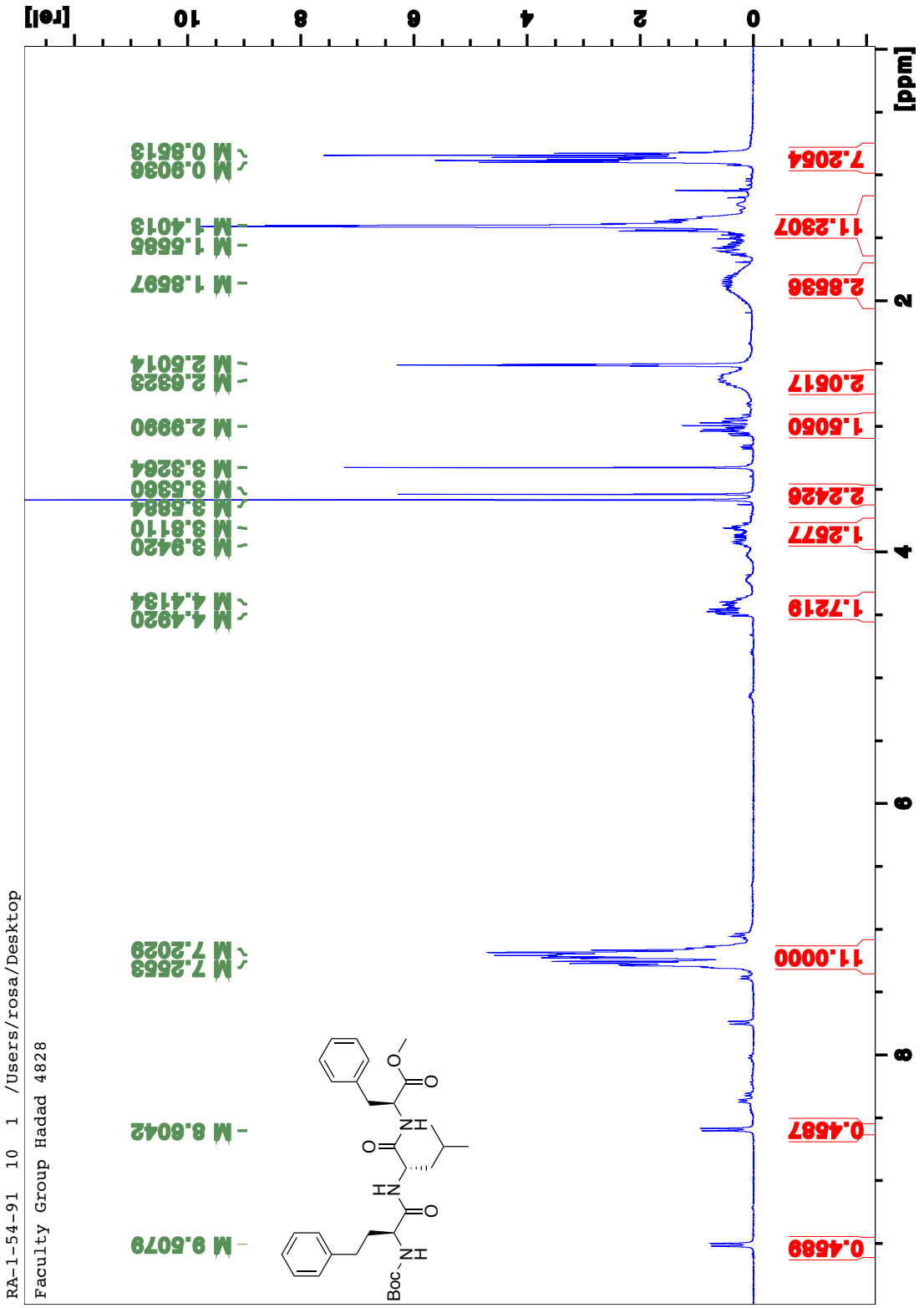
1.0528
0.9770
5.7724
0.9141
M 0.8058
M 0.9980
M 1.4156
M 1.6193
M 2.5053
M 2.4442
M 3.8200
M 4.0431
M 4.2570
M 4.8171
M 5.0309
M 7.3793
M 7.8316
M 9.3592


RA-1-54-91 10 1 /Users/rosa/Desktop
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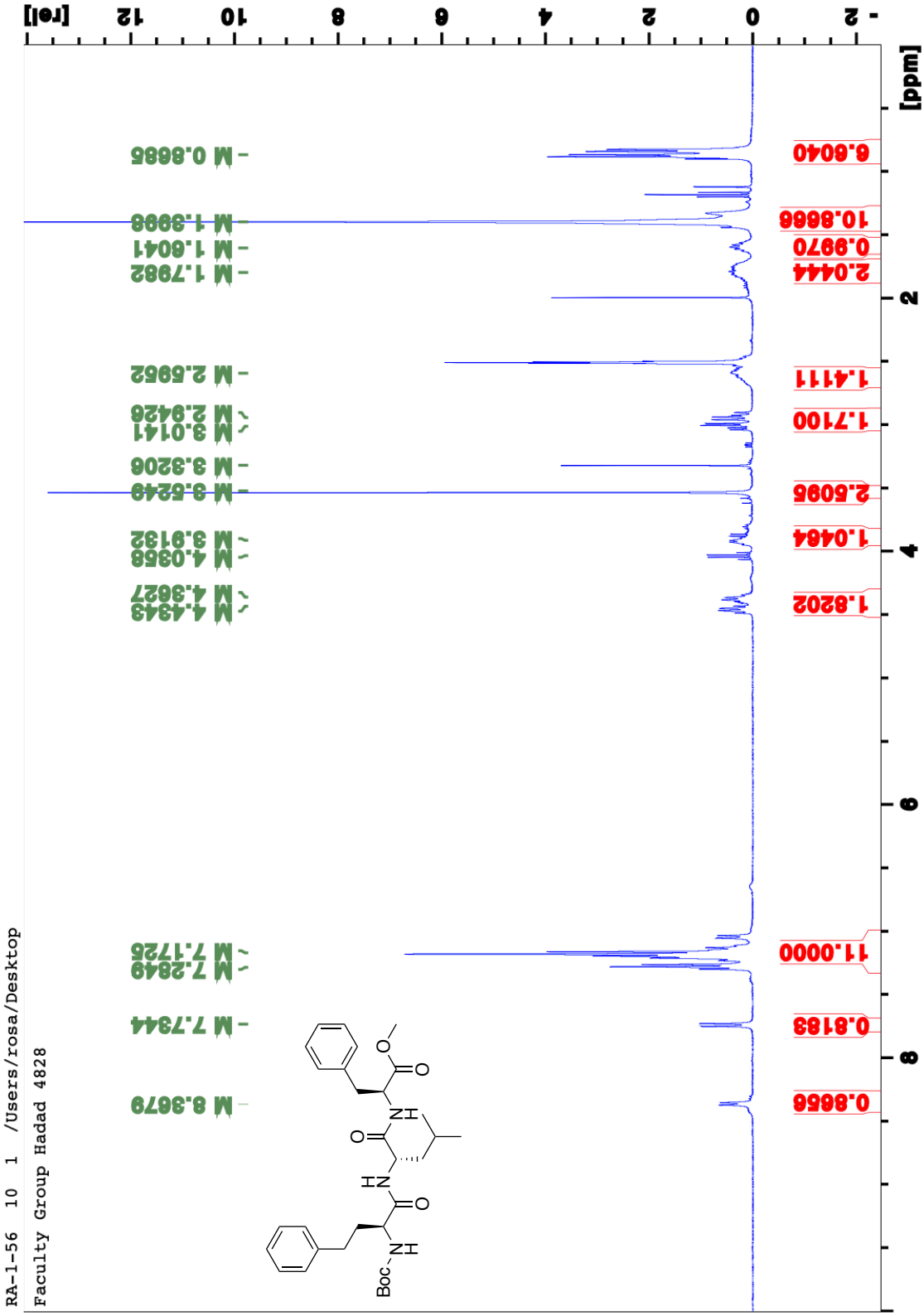
2.8536
2.0617
1.5060
2.2426
1.2577
1.7219
M 9.5079
M 8.6042
M 7.2653
M 7.2029
M 4.4920
M 4.4134
M 3.9420
M 3.8110
M 3.5884
M 3.5360
M 3.3264
M 2.9990
M 2.6323
M 2.5014
M 1.8597
M 1.5585
M 1.4013
M 0.9036
M 0.8613
Boc
NH
O
O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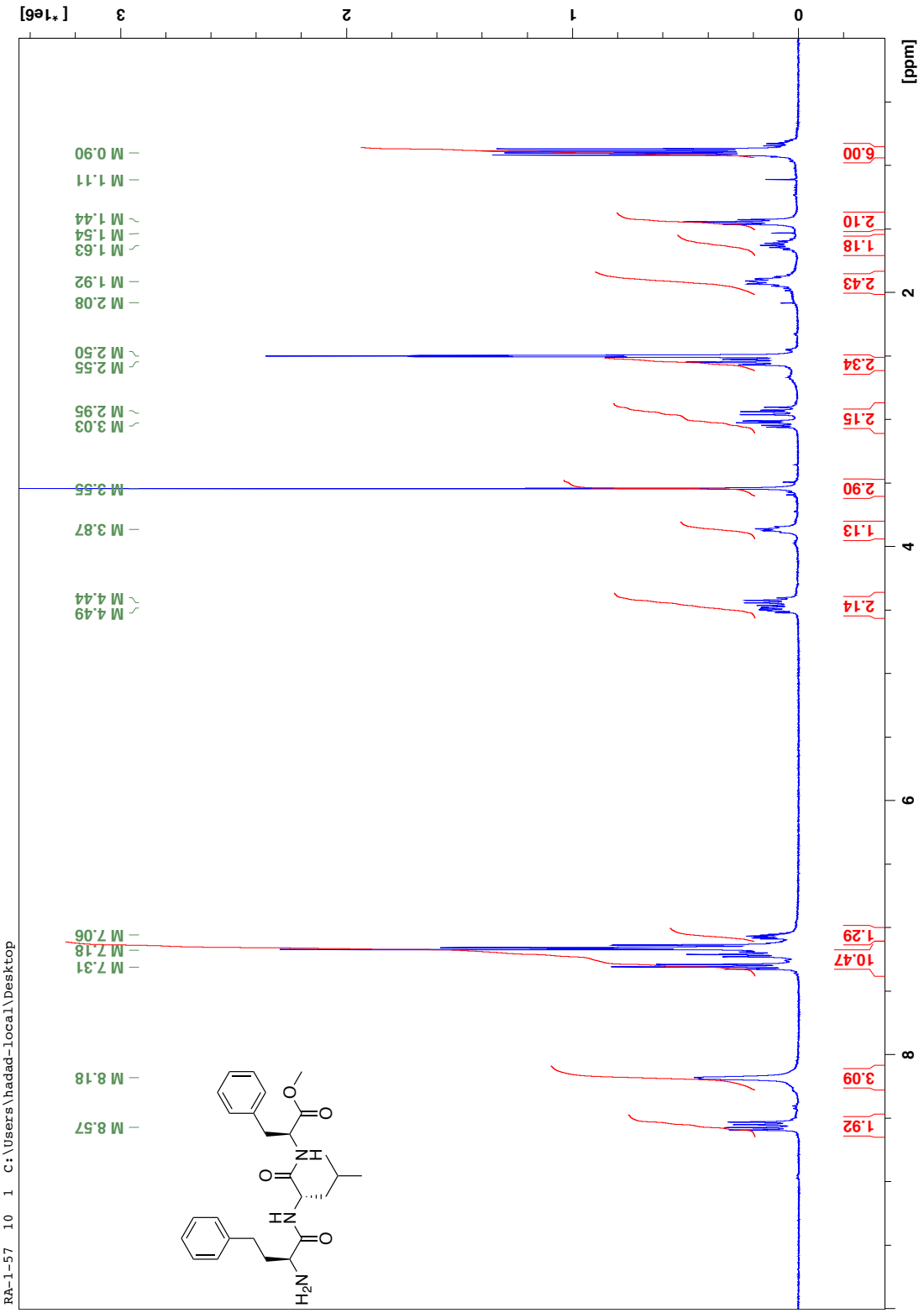
1.7100
2.5085
1.0464
1.8202
0.8656
0.8183
Boc


RA-1-57 10 1 C:\Users\hadad-local\Desktop
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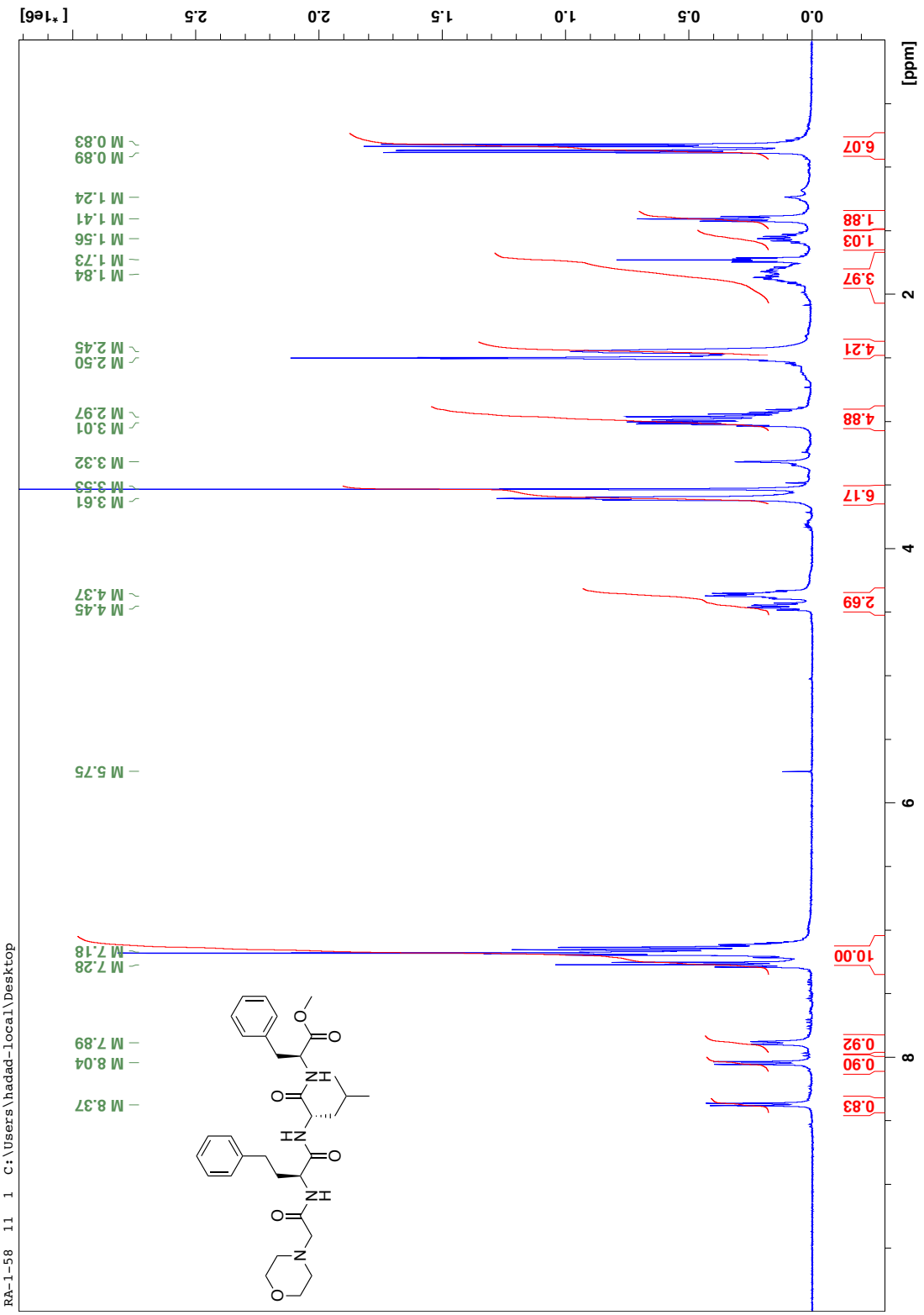
1.18
2.43
2.34
2.15
2.90
1.13
2.14
1.29
10.47
3.09
1.92
M 0.90
M 1.11
M 1.44
M 1.54
M 1.63
M 1.92
M 2.08
M 2.50
M 2.55
M 2.95
M 3.03
M 3.55
M 3.87
M 4.44
M 4.49
M 7.06
M 7.18
M 7.31
M 8.18
M 8.57


RA-1-58 11 1 C:\Users\hadad-local\Desktop
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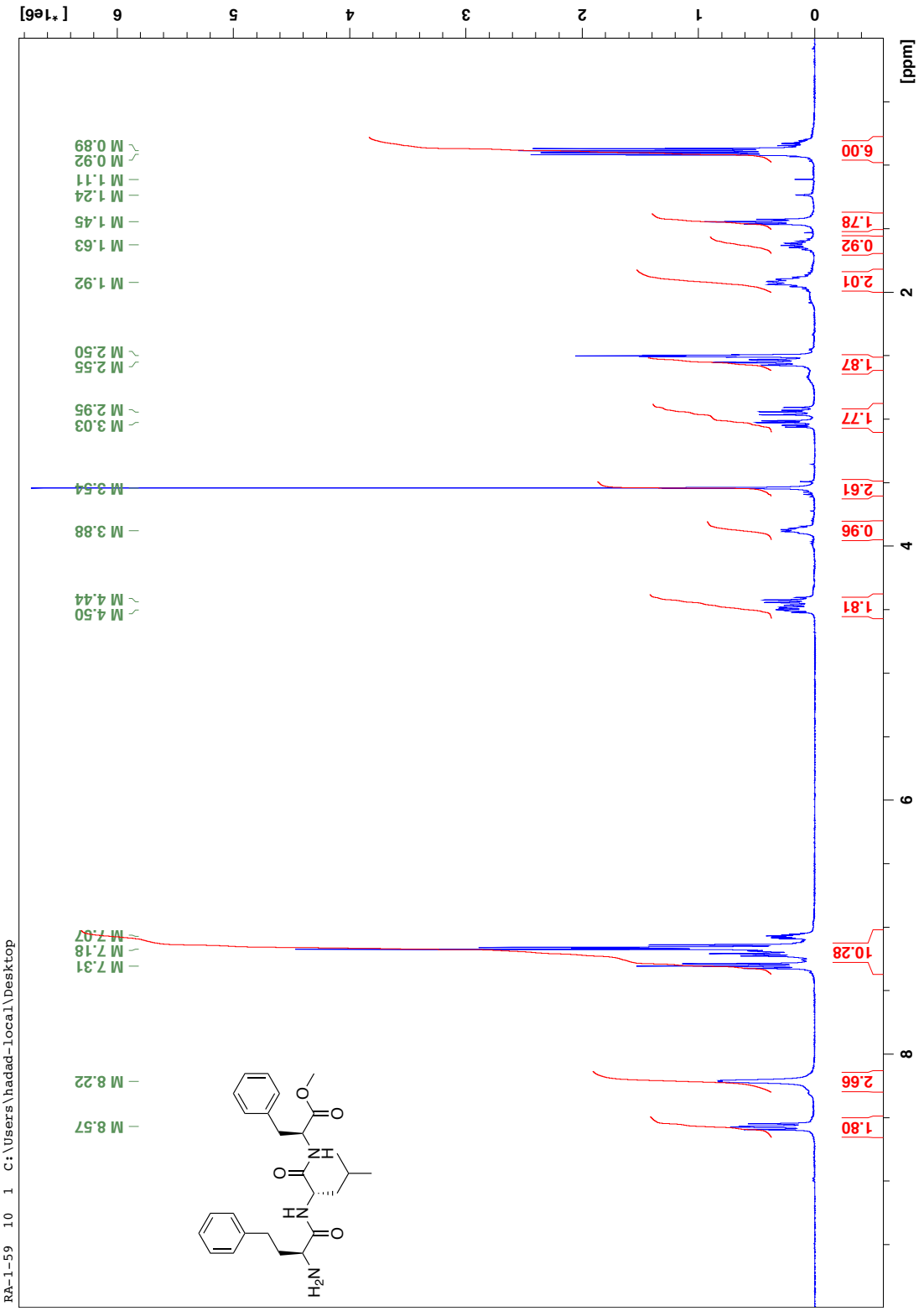
1.0
1.5
2.0
2.5
2
4
6
8
M 0.83
M 0.89
M 1.24
M 1.41
M 1.56
M 1.73
M 1.84
M 2.45
M 2.50
M 2.97
M 3.01
M 3.32
M 3.53
M 3.61
M 4.37
M 4.45
M 5.75
M 7.18
M 7.28
M 7.89
M 8.04
M 8.37
6.07
1.88
1.03
3.97
4.21
4.88
6.17
2.69
10.00
0.92
0.90
0.83


RA-1-59 10 1 C:\Users\hadad-local\Desktop
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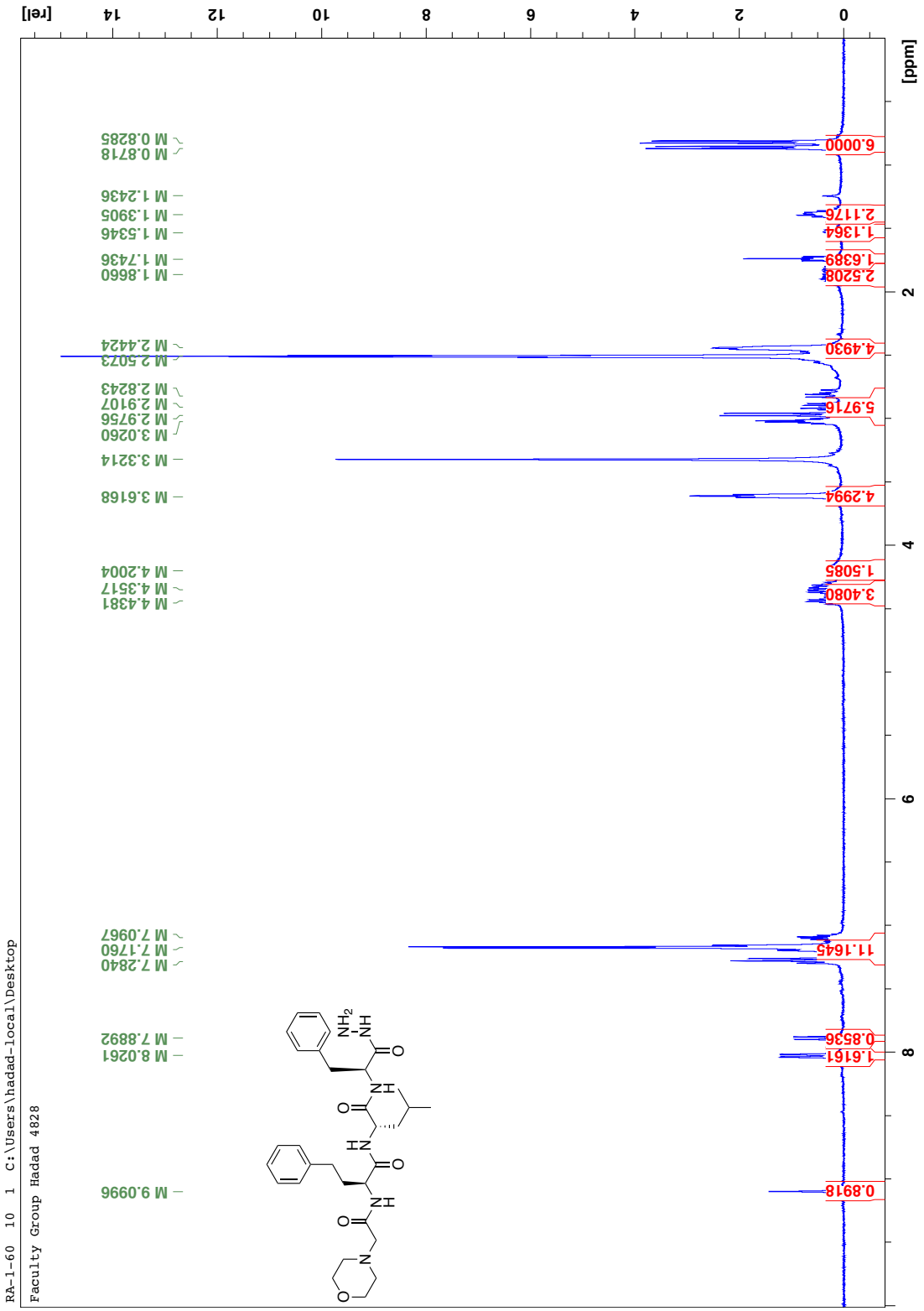
M 0.92
M 1.11
M 1.24
M 1.45
M 1.63
M 1.92
M 2.50
M 2.55
M 2.95
M 3.03
M 3.54
M 3.88
M 4.44
M 4.50
M 7.07
M 7.18
M 7.31
M 8.22
M 8.57
6.00
1.78
0.92
2.01
1.87
1.77
2.61
0.96
1.81
10.28
2.66
1.80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Faculty Group Hadad 4828
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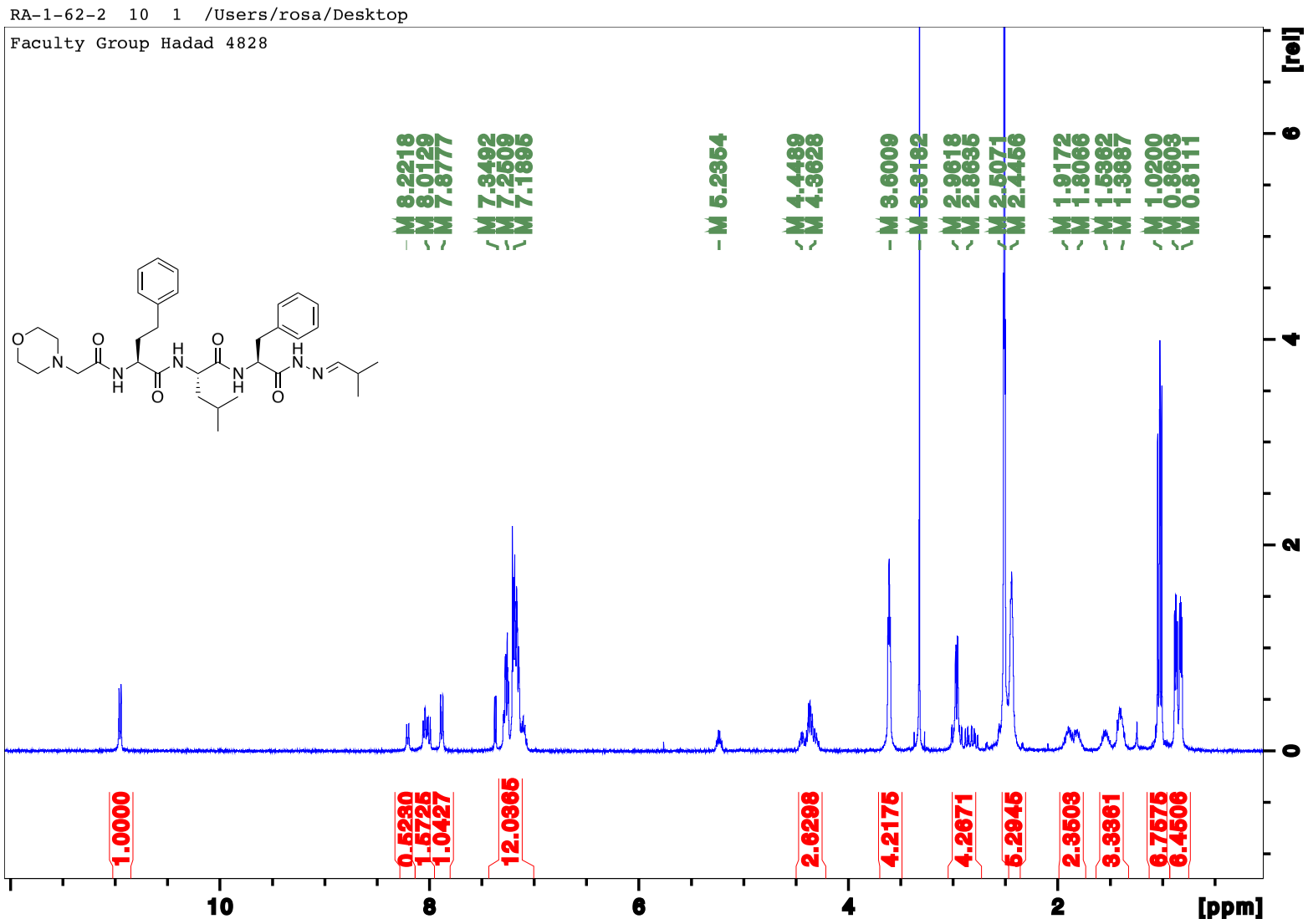
3.4080
1.5085
4.2994
5.9716
4.4930
2.5208
1.6389
1.1364
2.1176
6.0000
M 9.0996
M 8.0261
M 7.8892
M 7.2840
M 7.1760
M 7.0967
M 4.4381
M 4.3517
M 4.2004
M 3.6168
M 3.3214
M 3.0260
M 2.9756
M 2.9107
M 2.8243
M 2.5073
M 2.4424
M 1.8660
M 1.7436
M 1.5346
M 1.3905
M 1.2436
M 0.8718
M 0.8285


RA-1-62-2 10 1 /Users/rosa/Desktop
Faculty Group Hadad 4828
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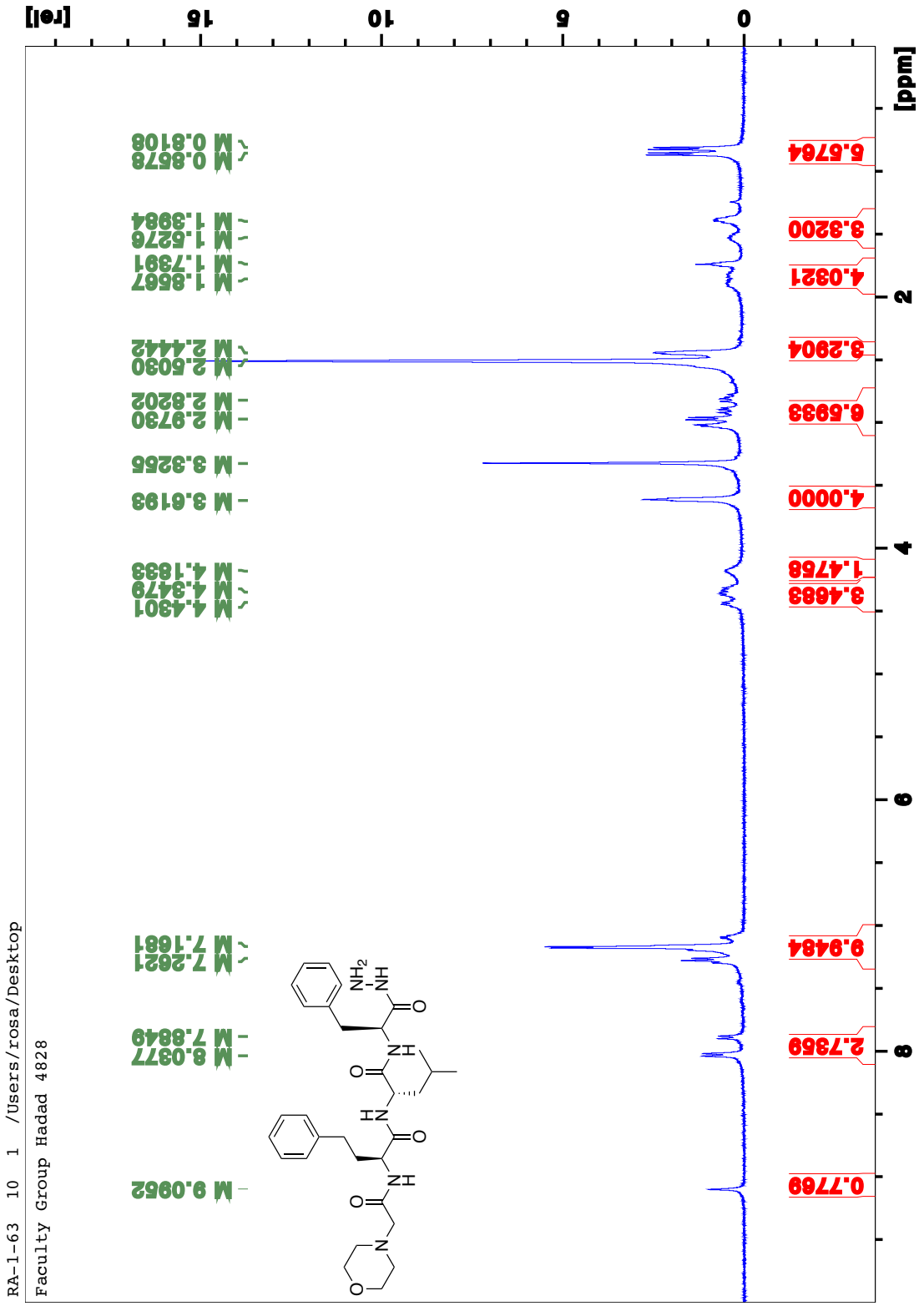
M 8.0129
M 7.8777
M 7.3492
M 7.2509
M 7.1895
M 5.2354
M 4.4489
M 4.3628
M 3.6009
M 3.3182
M 2.9618
M 2.8835
M 2.5071
M 2.4456
M 1.9172
M 1.8066
M 1.5362
M 1.3887
M 1.0200
M 0.8603
M 0.8111
1.0000
0.5230
1.5725
1.0427
12.0365
2.6298
4.2175
4.2671
5.2945
2.3503
3.3361
6.7575
6.4506
10
8
6
4
2
[ppm]
0
2
4
6
[rel]


RA-1-63 10 1 /Users/rosa/Desktop
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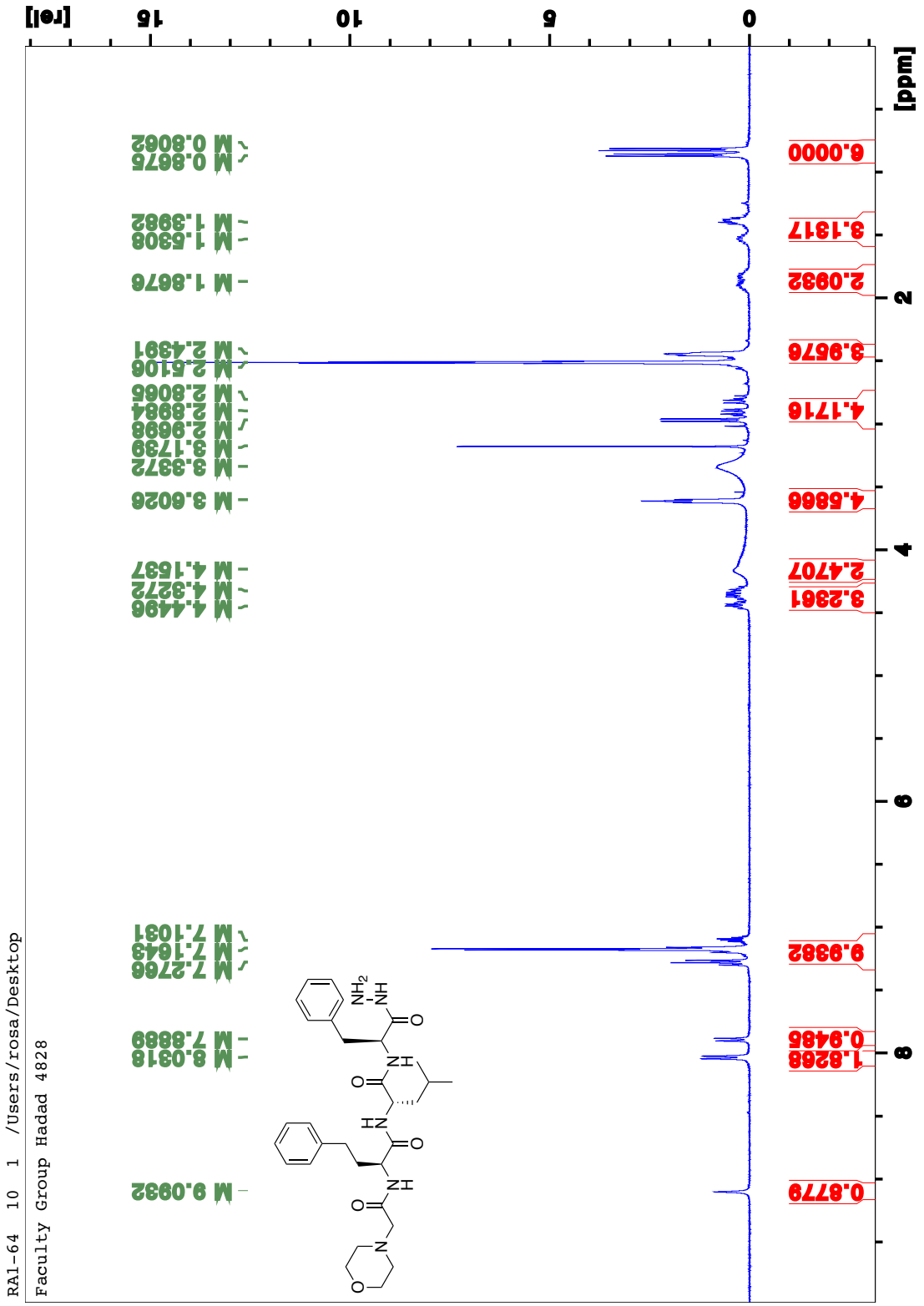
9.9484
3.4683
1.4768
4.0000
6.6933
3.2904
4.0321
3.3200
5.6764
9.0852
7.8849
8.0377
7.2621
7.1681
4.4301
4.3479
4.1833
3.6193
3.3265
2.9730
2.8202
2.6030
2.4442
1.8667
1.7391
1.6276
1.3884
0.8678
0.8108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2
4
6
8
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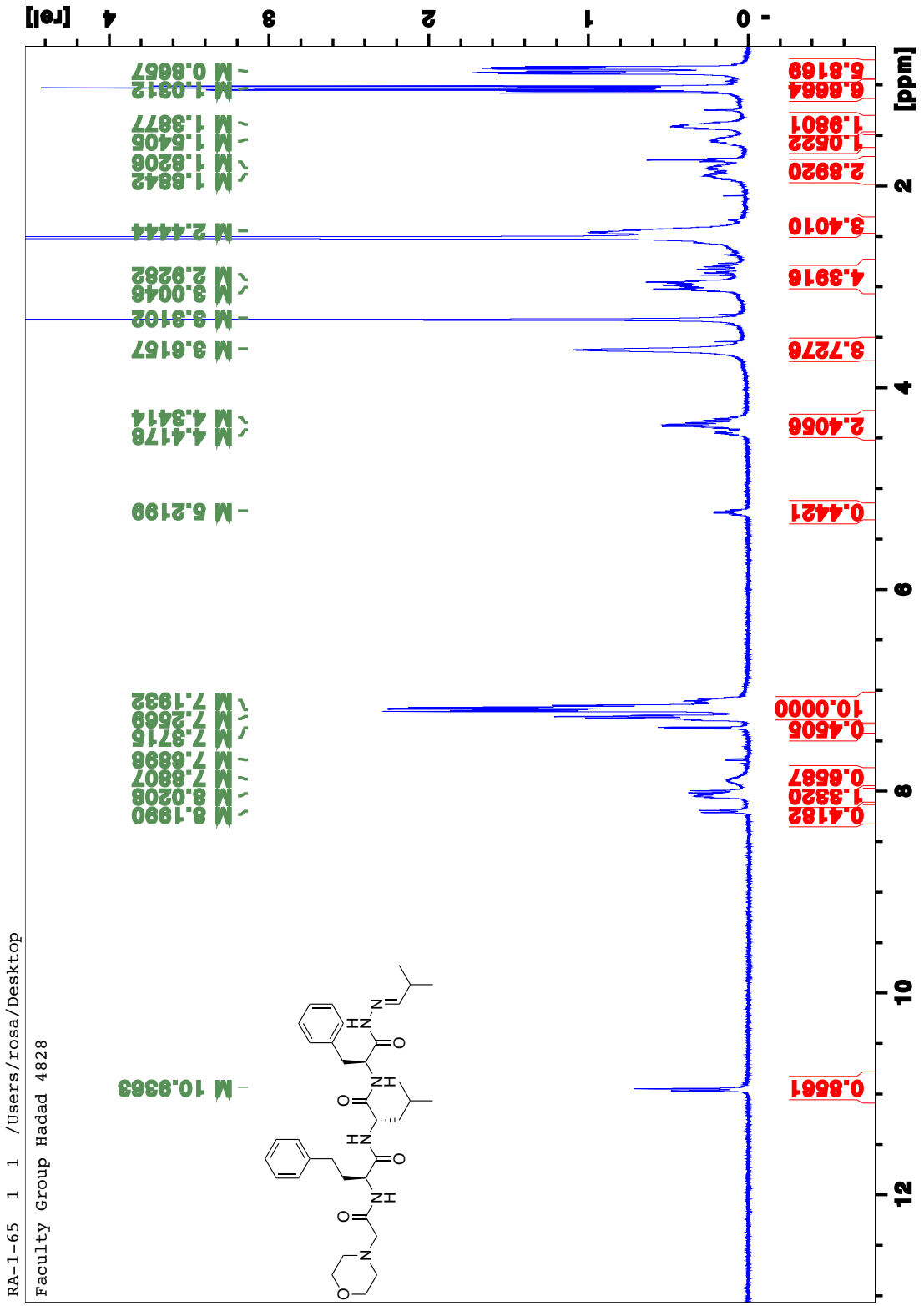
2.0932
3.9576
4.1716
4.5866
2.4707
3.2361
9.0382
1.8268
0.9485
0.8779
M 0.8675
M 0.8062
M 1.5308
M 1.3982
M 1.8676
M 2.4391
M 2.6106
M 2.8065
M 2.8984
M 2.9698
M 3.1739
M 3.3372
M 3.6026
M 4.1637
M 4.3272
M 4.4496
M 7.1031
M 7.1643
M 7.2766
M 7.8889
M 8.0318
M 9.0932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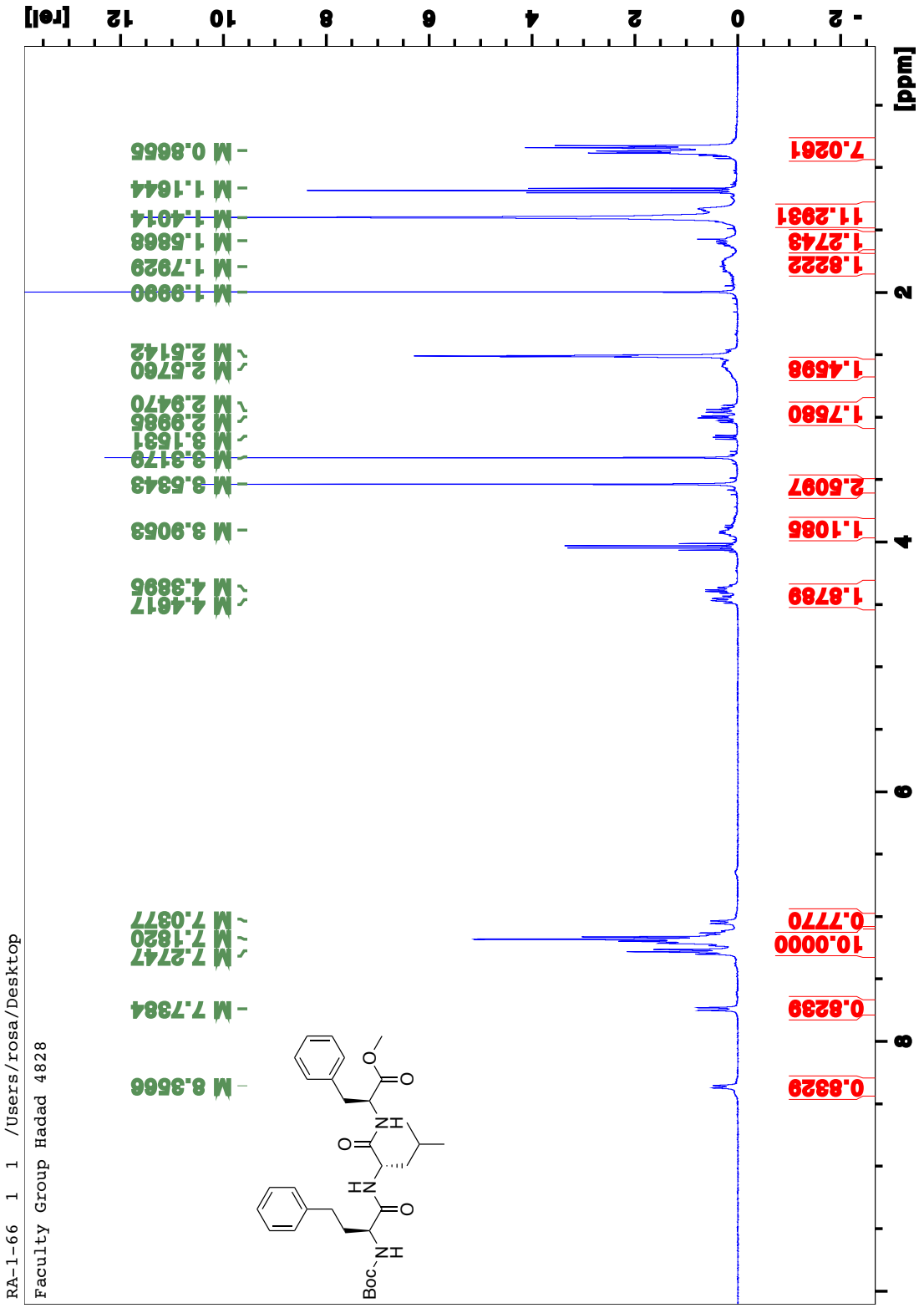
3.4010
4.3916
3.7276
2.4056
0.4421
10.0000
0.4505
0.4182
1.3320
0.8567
M 10.9363
M 8.1990
M 8.0208
M 7.8807
M 7.6898
M 7.3716
M 7.2569
M 7.1932
M 5.2199
M 4.4178
M 4.3414
M 3.6167
M 3.3102
M 3.0046
M 2.9282
M 2.4444
M 1.8842
M 1.8206
M 1.5406
M 1.3877
M 1.0312
M 0.8667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Faculty Group Hadad 4828
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1.1065
1.8789
0.7770
10.0000
0.8239
0.8329
8.3566
7.7384
7.2747
7.1820
7.0377
4.4617
4.3896
3.9053
3.5343
3.1791
2.9965
2.9470
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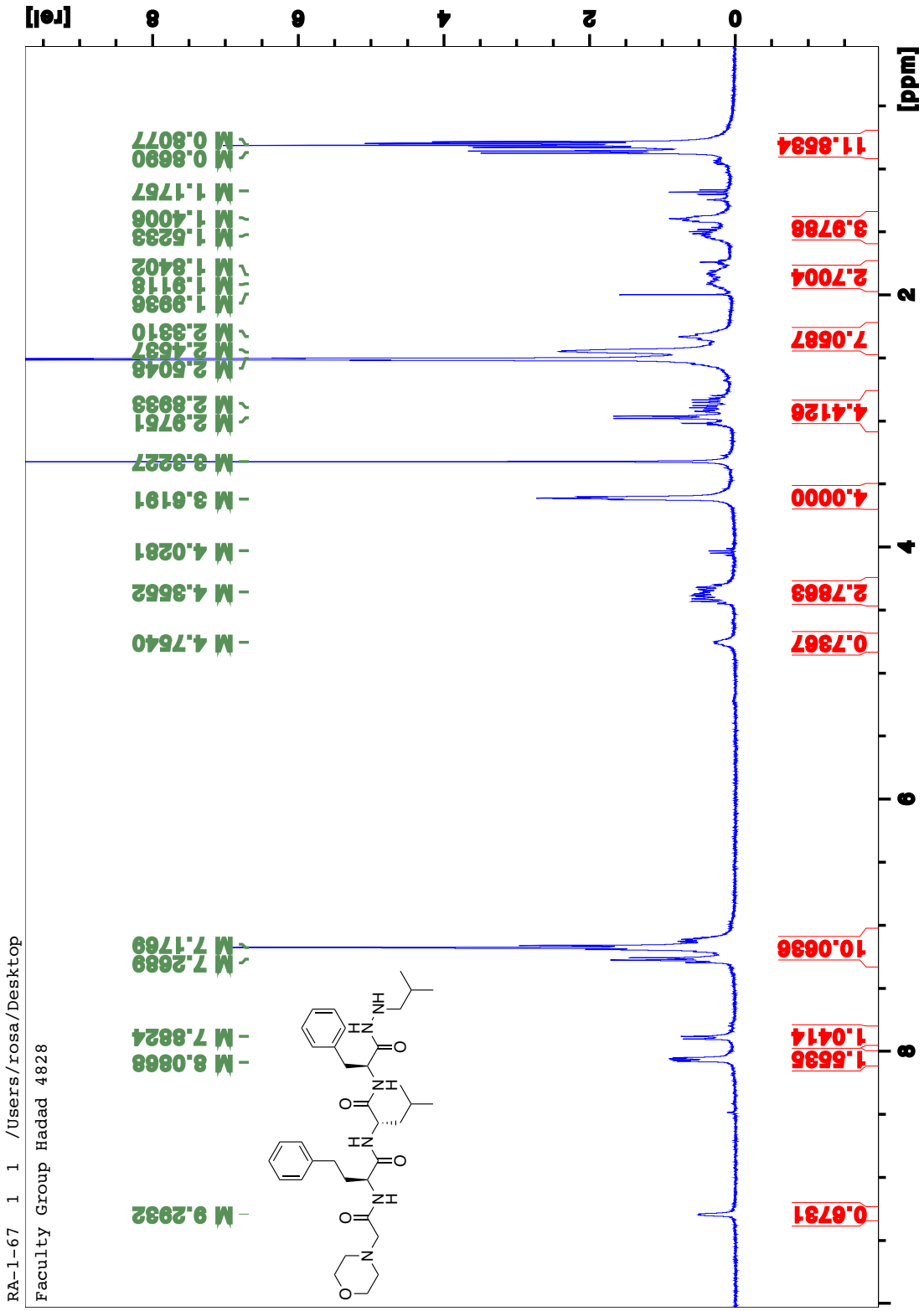
2.5142
1.8990
1.7929
1.5868
1.4014
1.1644
0.8656
Boc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4.0000
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0.7367
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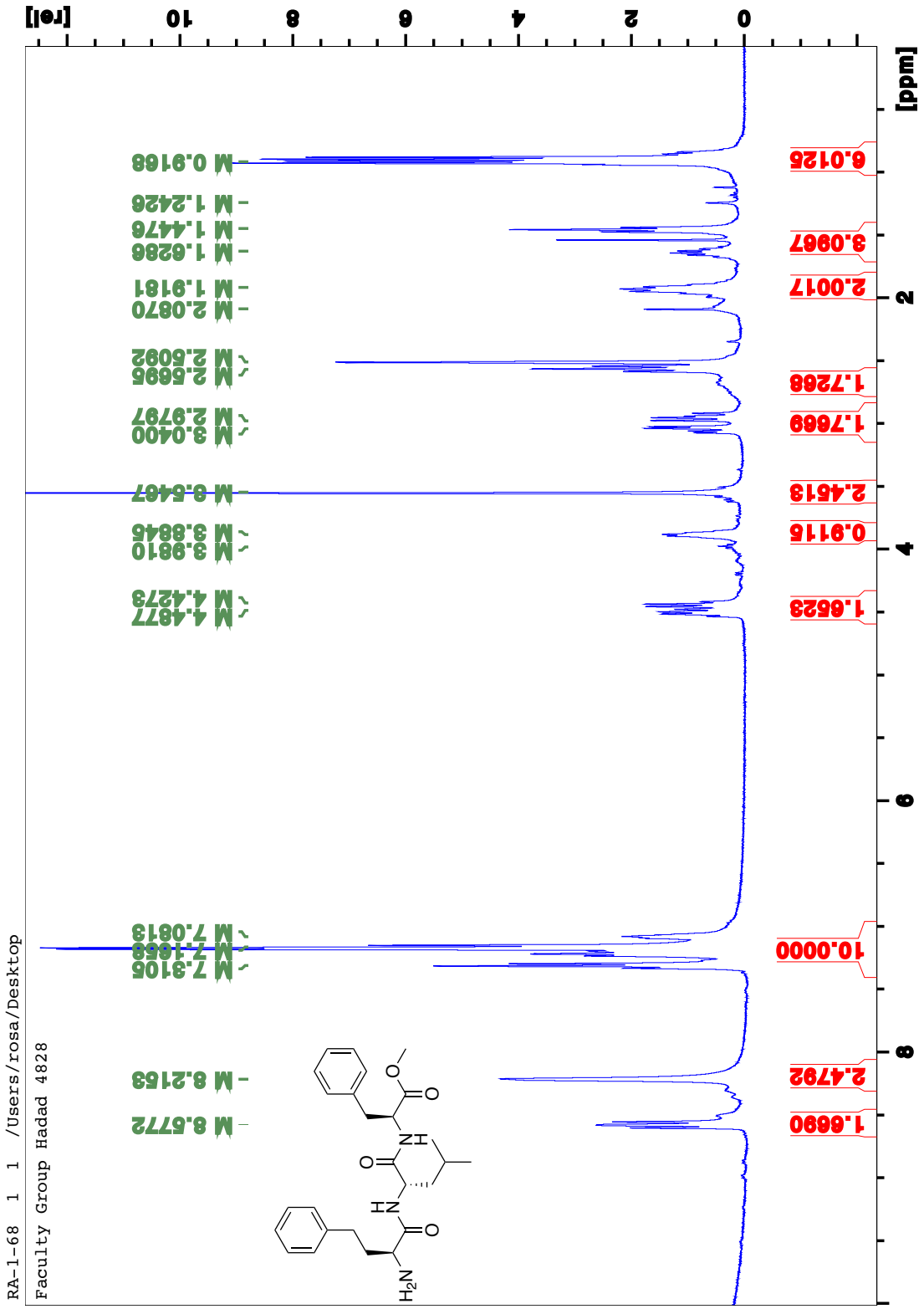
1.5536
0.6731
M 0.8077
M 0.8690
M 1.1757
M 1.4006
M 1.6233
M 1.8402
M 1.9118
M 1.9936
M 2.3310
M 2.4637
M 2.5048
M 2.8933
M 2.9761
M 3.8227
M 3.6191
M 4.0281
M 4.3562
M 4.7540
M 7.1769
M 7.2689
M 7.8824
M 8.0868
M 9.2932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1.7669
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1.6523
10.0000
2.4792
1.6690
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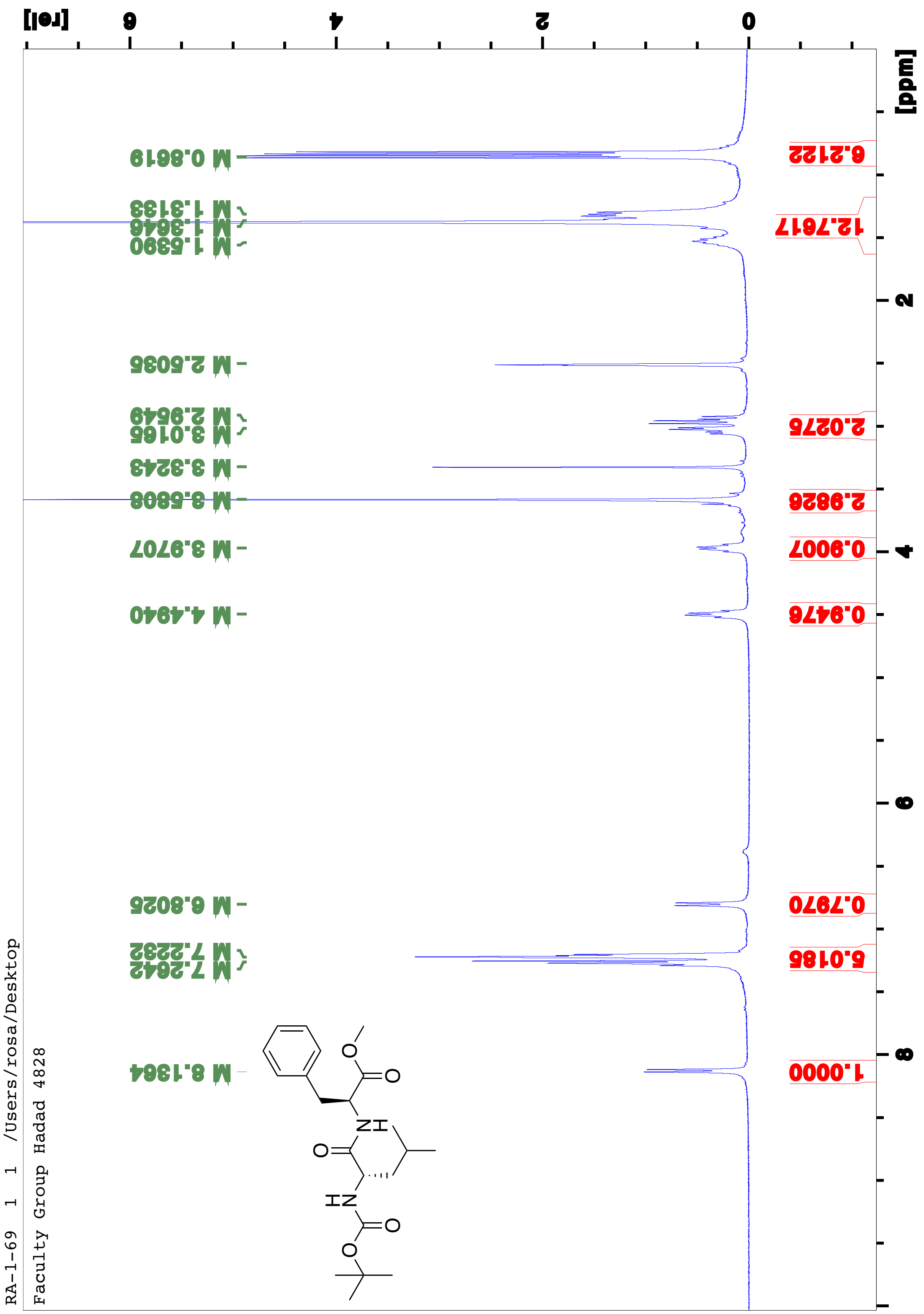
M 1.2426
M 1.4476
M 1.6286
M 1.9181
M 2.0870
M 2.5092
M 2.6696
M 2.9797
M 3.0400
M 3.5467
M 3.8846
M 3.9810
M 4.2273
M 4.4877
M 7.0813
M 7.1668
M 7.3105
M 8.2153
M 8.5772
O
O
NH
O
NH
O
H_2N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M 2.9549
M 3.0166
M 3.3243
M 3.5808
M 3.9707
M 4.4940
M 6.8025
M 7.2232
M 7.2642
M 8.1364
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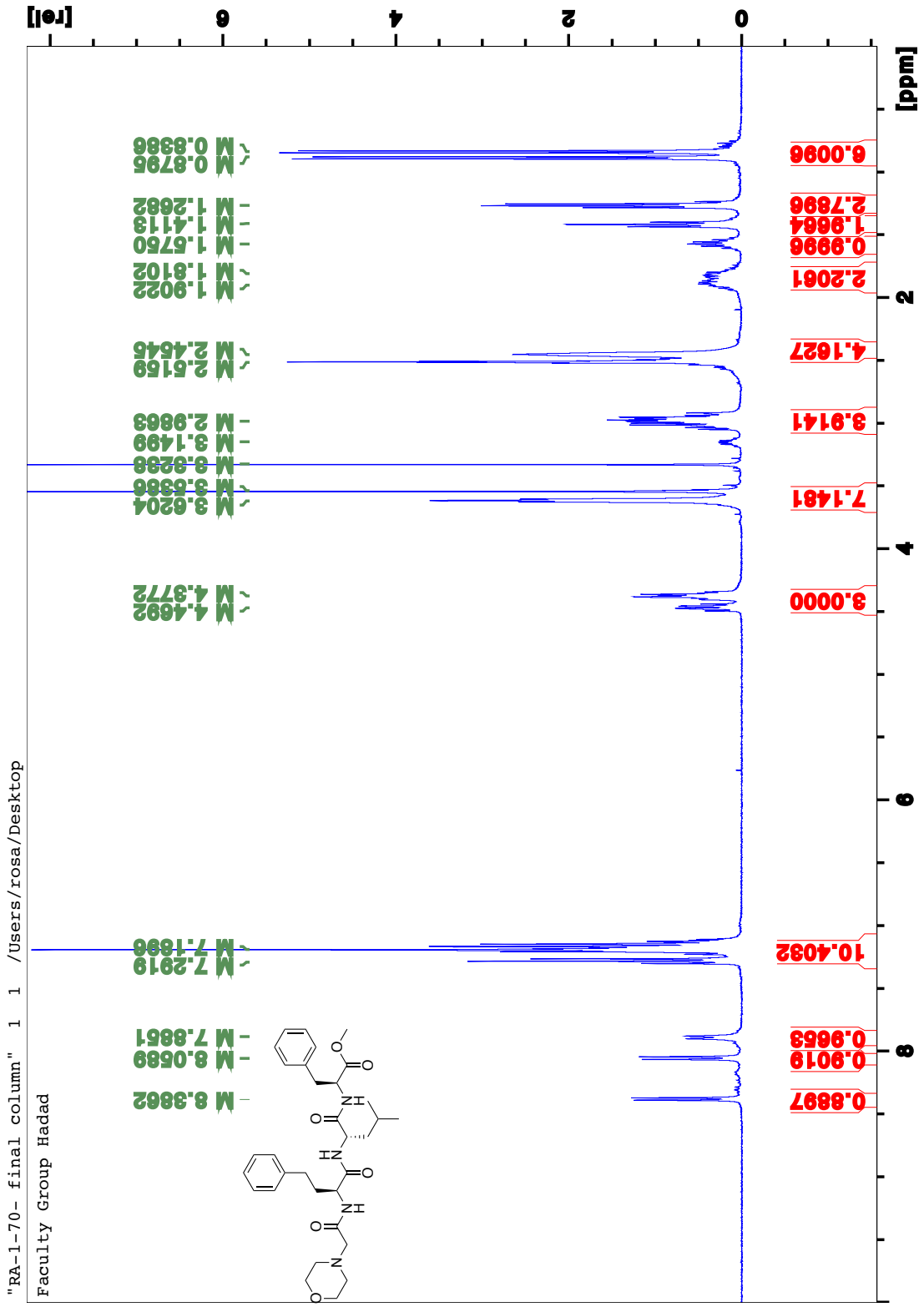
12.7617
2.0275
2.9826
0.9007
0.9476
0.7970
5.0186
1.0000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4.1627
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3.0000
2.7896
2.2061
1.9864
0.9996
0.9019
0.8658
0.8397
M 0.8796
M 0.8386
M 1.2682
M 1.4113
M 1.5760
M 1.8102
M 1.9022
M 2.4545
M 2.6159
M 2.9863
M 3.1499
M 3.8288
M 3.8386
M 3.8204
M 4.3772
M 4.4692
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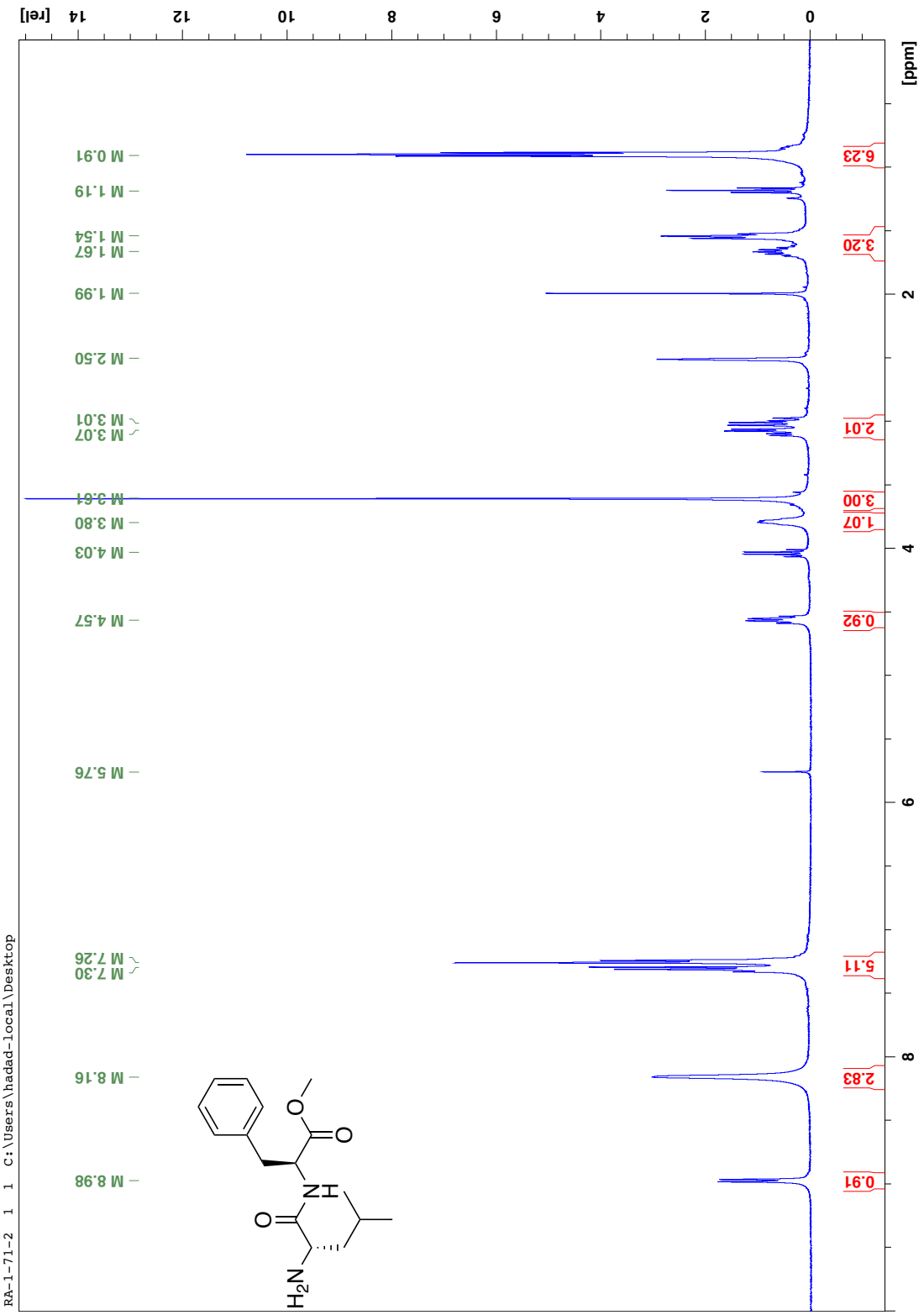
M 7.8861
M 8.0589
M 8.3862


RA-1-71-2 1 1 C:\Users\hadad-local\Desktop
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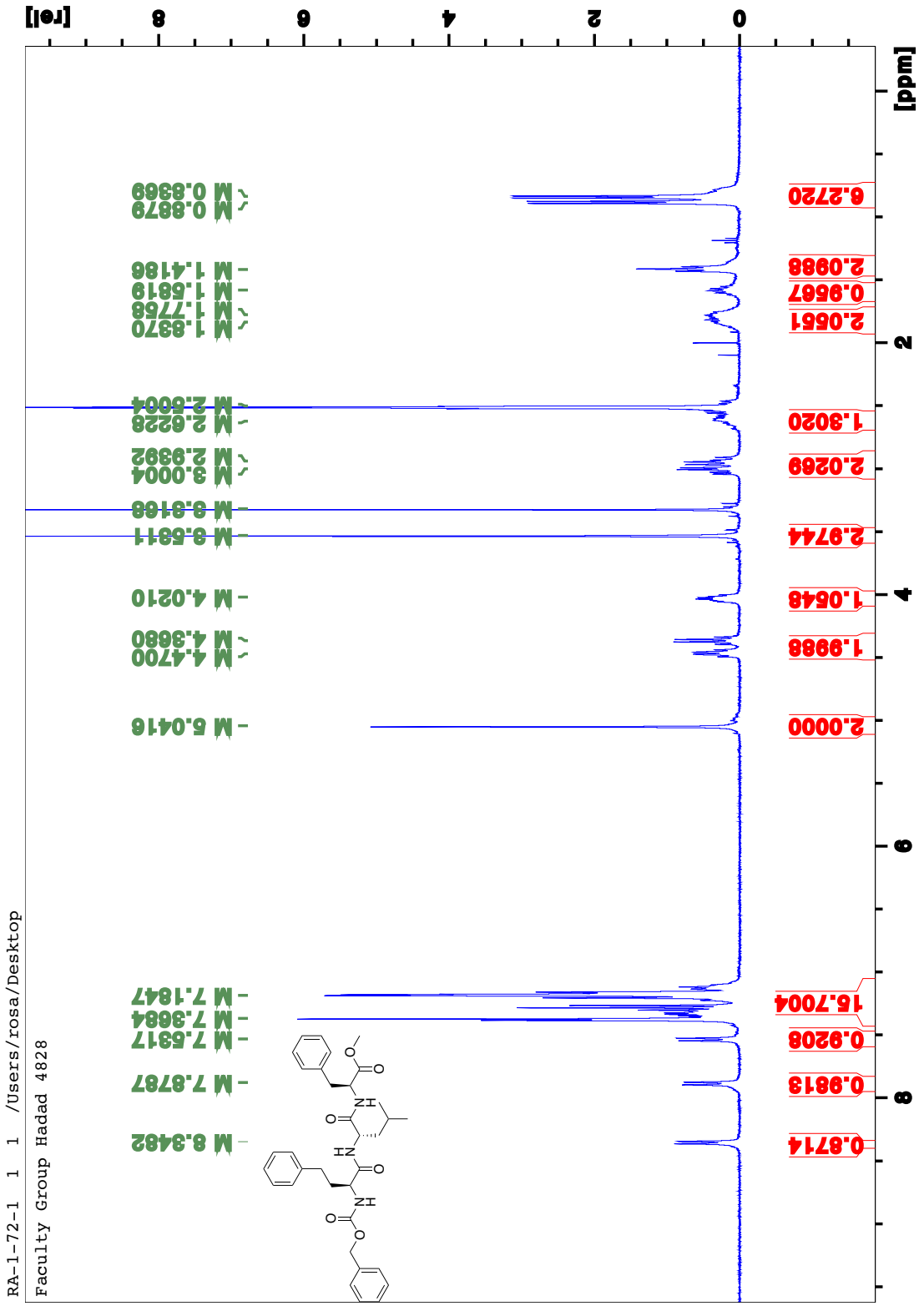
M 3.07
M 3.61
M 3.80
M 4.03
M 4.57
M 5.76
M 7.26
M 7.30
M 8.16
M 8.98
0.91
2.83
5.11
0.92
1.07
3.00
2.01
3.20
6.23
O
O
NH
O
H2N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2.9744
2.0269
1.3020
2.0651
0.9567
2.0988
6.2720
8.3482
7.8787
7.6317
7.3684
7.1847
5.0416
4.4700
4.3680
4.0210
3.6311
3.3168
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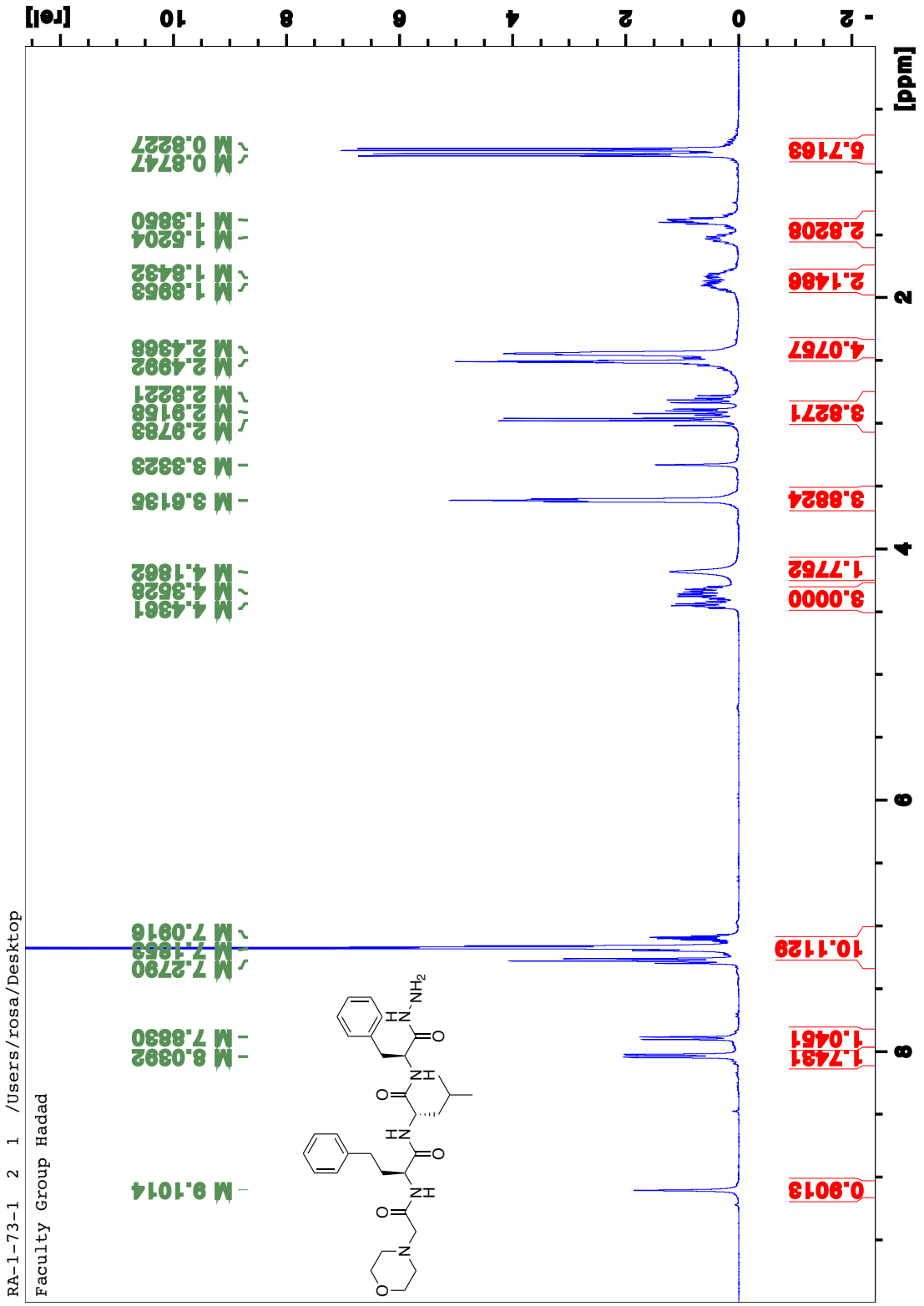
0.8369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Faculty Group Hadad
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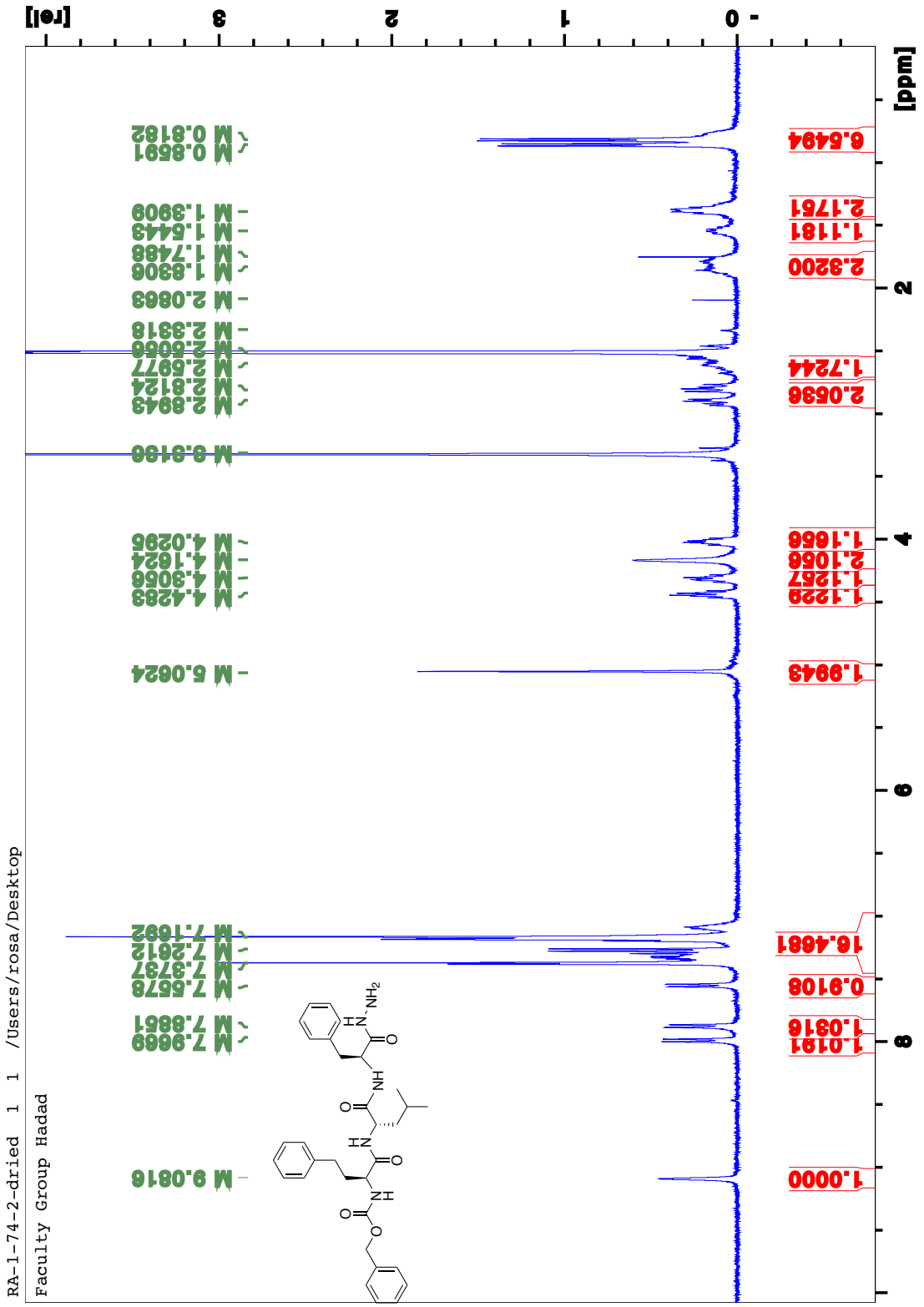
4.0767
2.1486
2.8208
6.7163
10.1129


RA-1-74-2-dried 1 1 /Users/rosa/Desktop
Faculty Group Hadad
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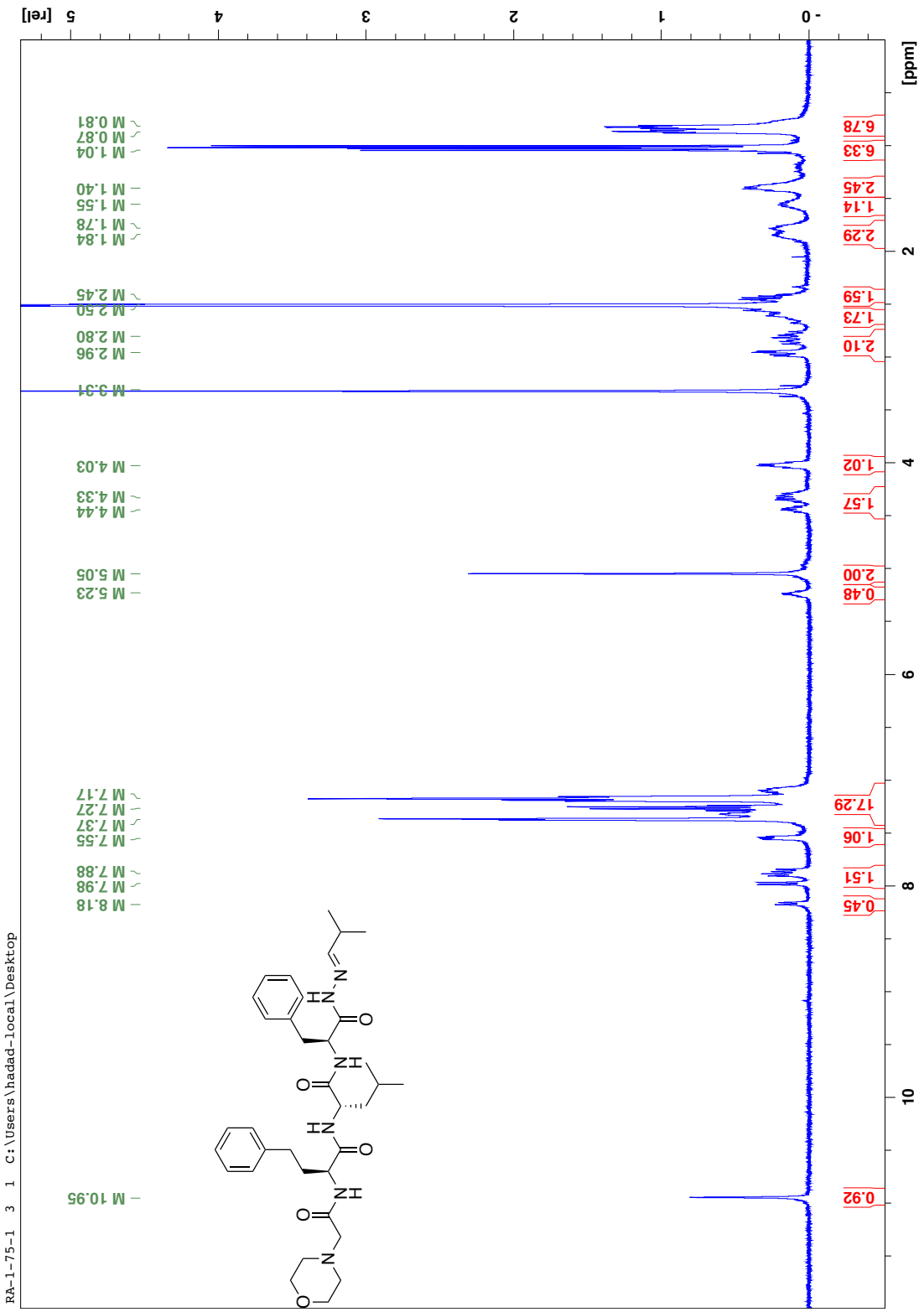
1.1181
2.8200
1.7244
2.0536
1.9943
1.1229
1.1257
2.1056
1.1656
9.0816
7.1682
7.2612
7.3737
7.6578
7.8861
7.9669
0.8182
0.8591
1.3909
1.6443
1.7488
1.8306
2.0863
2.3318
2.6056
2.6977
2.8124
2.8943
3.8136
4.0295
4.1624
4.3056
4.4283
5.0624


RA-1-75-1 3 1 C:\Users\hadad-local\Desktop
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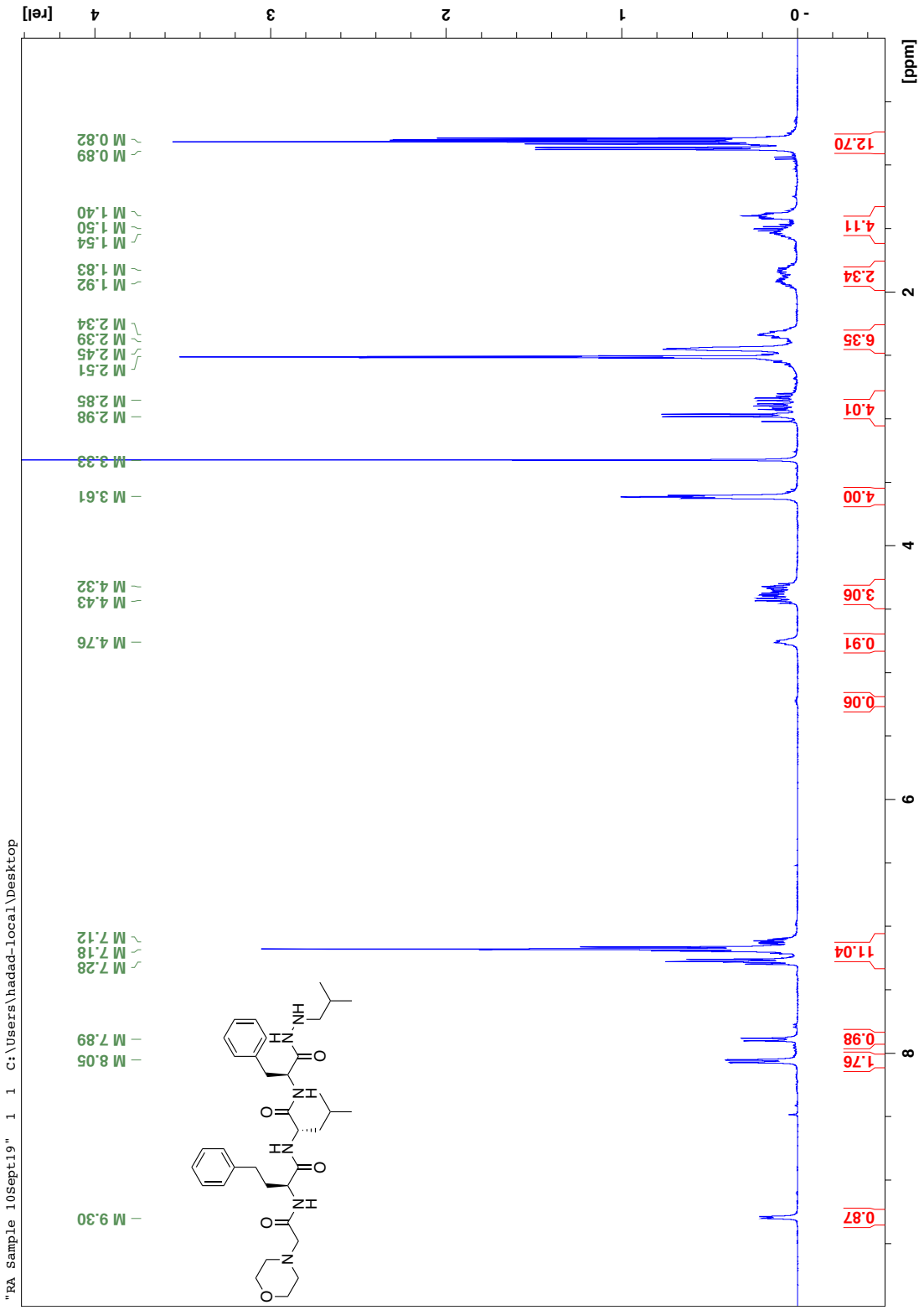
M 7.55
M 7.37
M 7.27
M 7.17
M 5.23
M 5.05
M 4.44
M 4.33
M 4.03
M 3.31
M 2.96
M 2.80
M 2.50
M 2.45
M 1.84
M 1.78
M 1.55
M 1.40
M 1.04
M 0.87
M 0.81
0.92
0.45
1.51
1.06
17.29
0.48
2.00
1.57
1.02
2.10
1.73
1.59
2.29
1.14
2.45
6.33
6.78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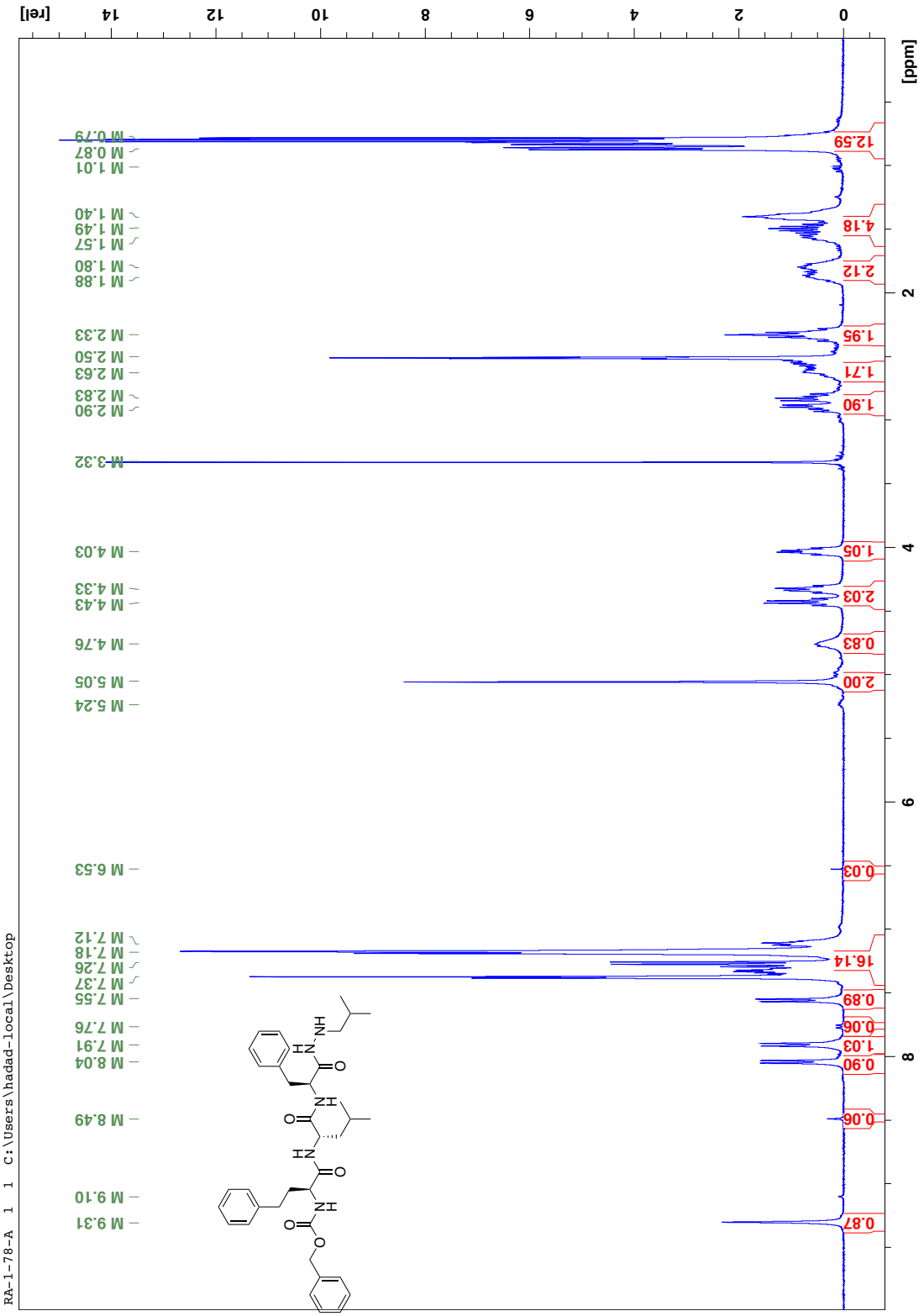
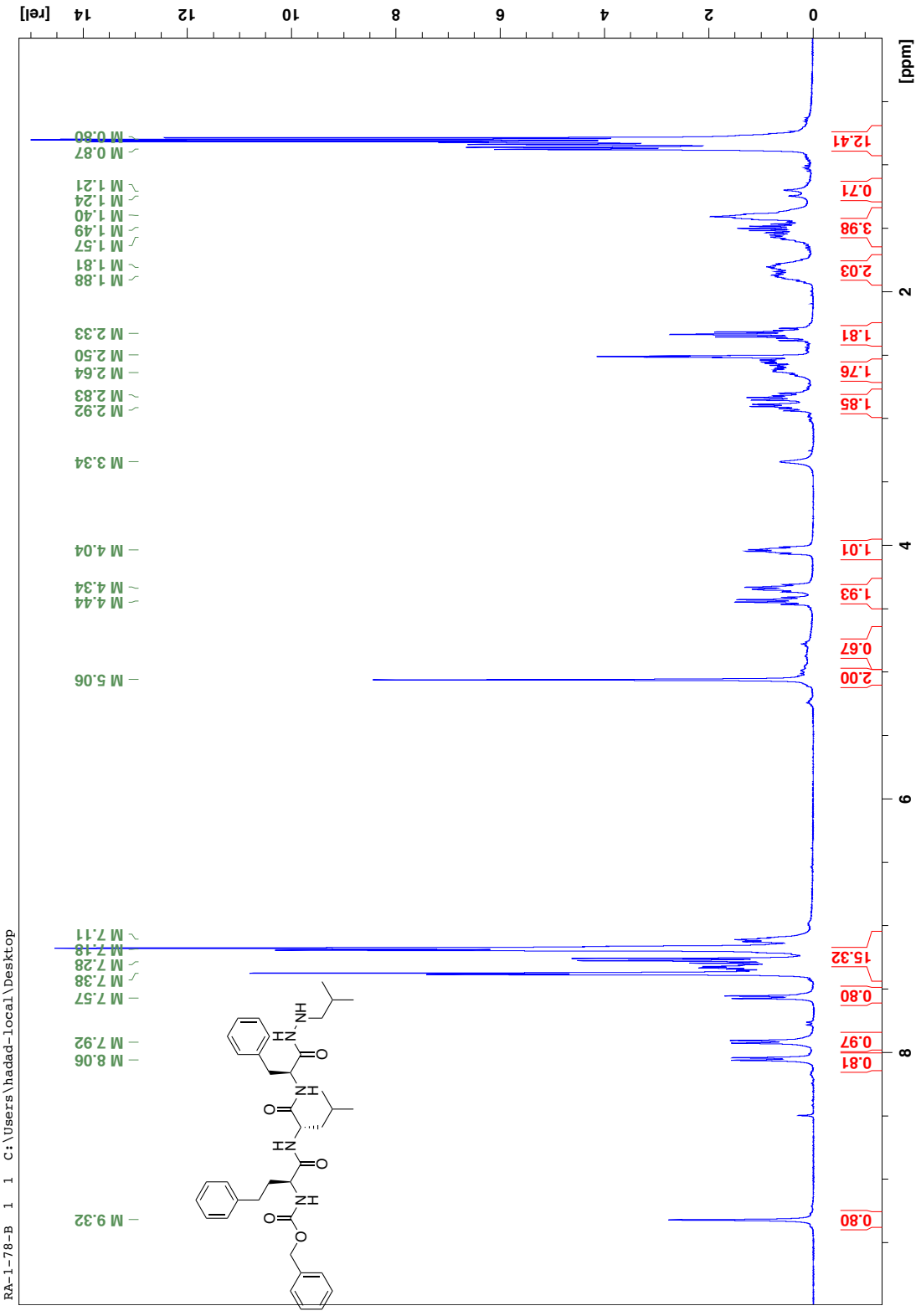
M 1.50
M 1.54
M 1.83
M 1.92
M 2.34
M 2.39
M 2.45
M 2.51
M 2.85
M 2.98
M 3.33
M 3.61
M 4.32
M 4.43
M 4.76
M 7.12
M 7.18
M 7.28
M 7.89
M 8.05
12.70
4.11
2.34
6.35
4.01
4.00
3.06
0.91
0.06
11.04
1.76
0.98
0.87


RA-1-78-A 1 1 C:\Users\hadad-local\Desktop
[ppm]
[rel]
12.59
4.18
2.12
1.95
1.71
1.90
3.32
1.05
2.03
0.83
2.00
0.03
16.14
0.89
0.06
1.03
0.90
0.06
0.87
M 0.79
M 0.87
M 1.01
M 1.40
M 1.49
M 1.57
M 1.80
M 1.88
M 2.33
M 2.50
M 2.63
M 2.83
M 2.90
M 4.03
M 4.33
M 4.43
M 4.76
M 5.05
M 5.24
M 6.53
M 7.12
M 7.18
M 7.26
M 7.37
M 7.55
M 7.76
M 7.91
M 8.04
M 8.49
M 9.10
M 9.31


RA-1-78-B 1 1 C:\Users\hadad-local\Desktop
[rel]
[ppm]
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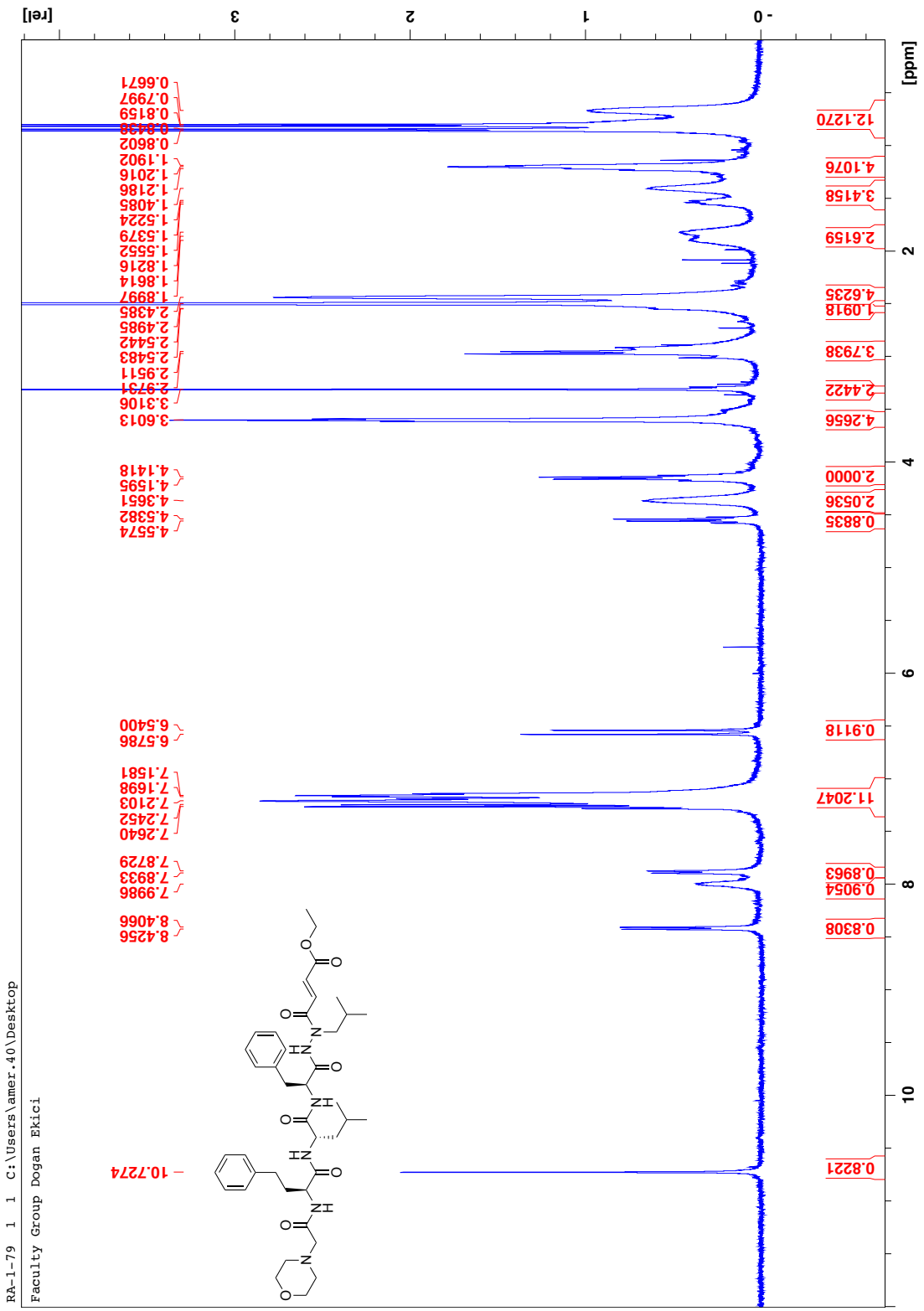
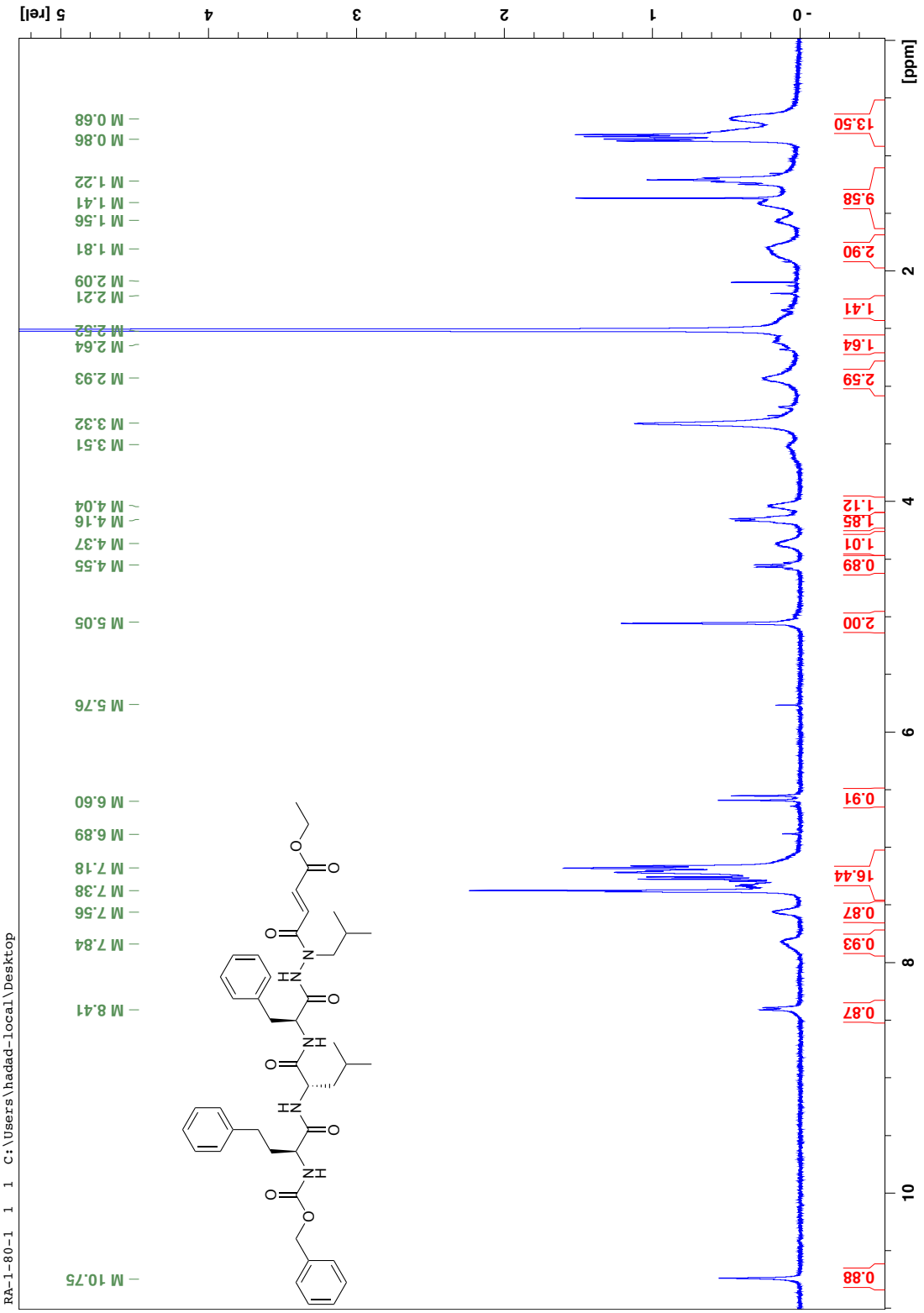
M 0.87
M 1.21
M 1.24
M 1.40
M 1.49
M 1.57
M 1.81
M 1.88
M 2.33
M 2.50
M 2.64
M 2.83
M 2.92
M 3.34
M 4.04
M 4.34
M 4.44
M 5.06
M 7.11
M 7.18
M 7.28
M 7.38
M 7.57
M 7.92
M 8.06
M 9.32
12.41
0.71
3.98
2.03
1.81
1.76
1.85
1.01
1.93
0.67
2.00
15.32
0.80
0.97
0.81
0.80


RA-1-79 1 1 C:\Users\amer.40\Desktop
Faculty Group Dogan Ekici
[rel]
[ppm]
10.7274
8.4256
8.4066
7.9986
7.8933
7.8729
7.2640
7.2452
7.2103
7.1698
7.1581
6.5786
6.5400
4.5574
4.5382
4.3651
4.1595
4.1418
3.6013
3.3106
2.9731
2.9511
2.5483
2.5442
2.4985
2.4385
1.8997
1.8614
1.8216
1.5552
1.5379
1.5224
1.4085
1.2186
1.2016
1.1902
0.8602
0.8438
0.8159
0.7997
0.6671
12.1270
4.1076
3.4158
2.6159
4.6235
1.0918
3.7938
2.4422
4.2656
2.0000
2.0536
0.8835
0.9118
11.2047
0.8963
0.9054
0.8308
0.8221


RA-1-80-1 1 1 C:\Users\hadad-local\Desktop
[ppm]
[rel]
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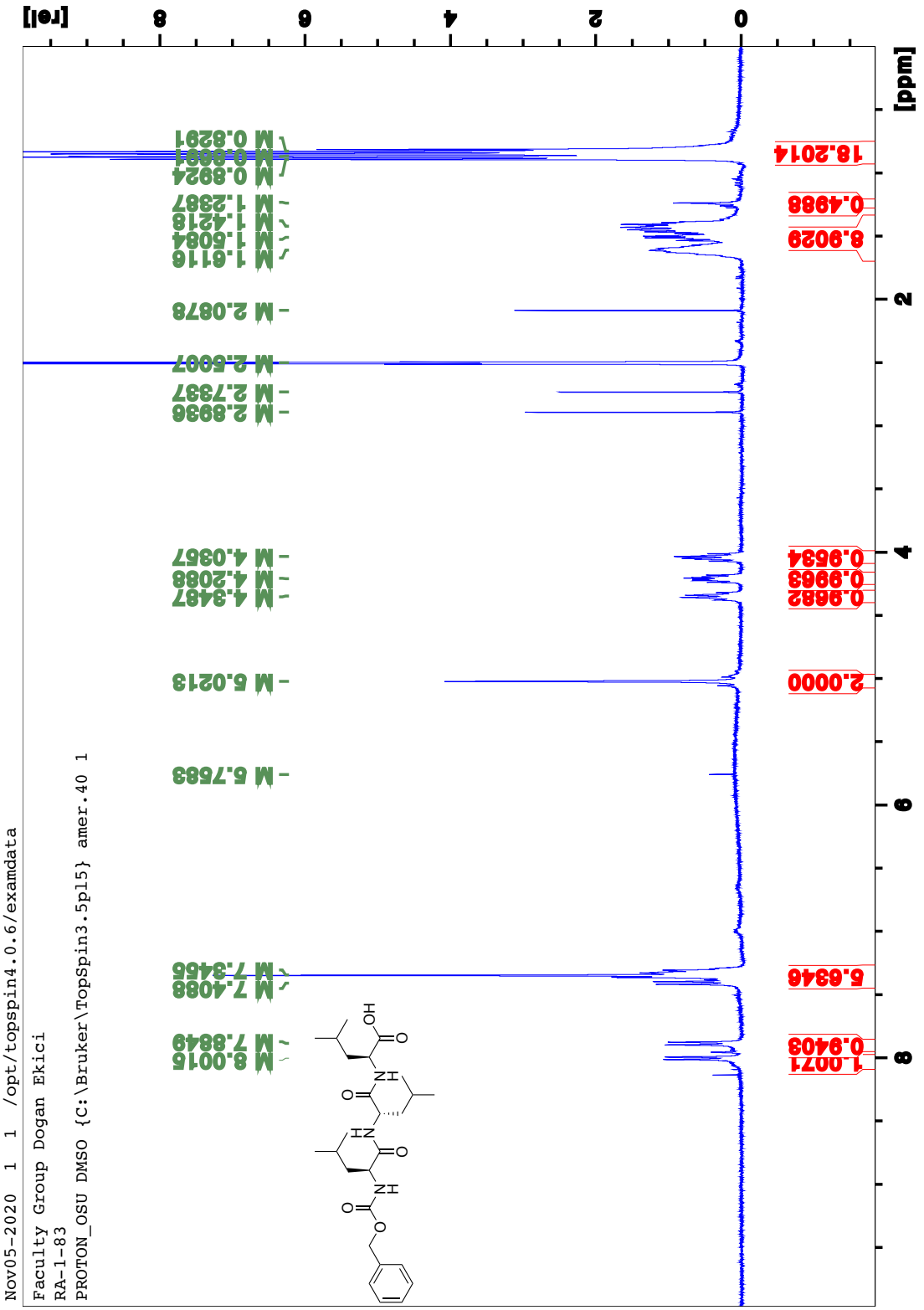
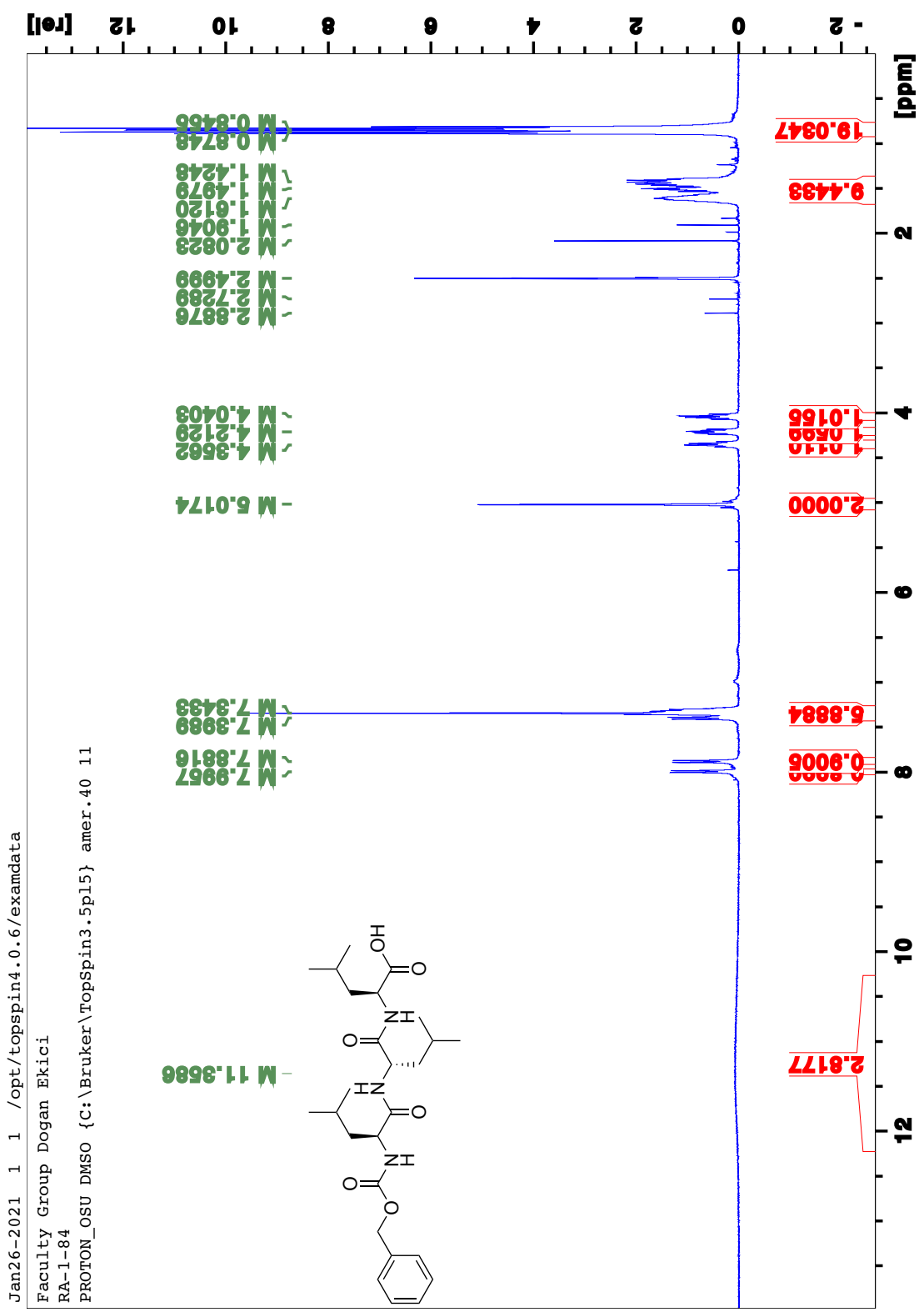
9.58
2.90
1.41
1.64
2.59
1.12
1.85
1.01
0.89
2.00
0.91
16.44
0.87
0.93
0.87
0.88
M 10.75
M 8.41
M 7.84
M 7.56
M 7.38
M 7.18
M 6.89
M 6.60
M 5.76
M 5.05
M 4.55
M 4.37
M 4.16
M 4.04
M 3.51
M 3.32
M 2.93
M 2.64
M 2.09
M 2.21
M 1.81
M 1.56
M 1.41
M 1.22
M 0.86
M 0.68


Nov05-2020 1 1 /opt/topspin4.0.6/examdata
Faculty Group Dogan Ekici
RA-1-83
PROTON_OSU DMSO {C:\Bruker\TopSpin3.5pl5} amer.40 1
[ppm]
[rel]
16.2014
0.4988
8.9029
0.9534
0.9963
0.9882
2.0000
5.6346
0.9403
1.0071
- M 8.0015
- M 7.8849
- M 7.4088
- M 7.3466
- M 5.7683
- M 5.0213
- M 4.3487
- M 4.2088
- M 4.0357
- M 2.8936
- M 2.7337
- M 2.6007
- M 2.0878
- M 1.6116
- M 1.5084
- M 1.4218
- M 1.2387
- M 0.8924
- M 0.8801
- M 0.8291


Jan26-2021 1 1 /opt/topspin4.0.6/examdata
Faculty Group Dogan Ekici
RA-1-84
PROTON_OSU DMSO {C:\Bruker\TopSpin3.5pl5} amer.40 11
[ppm]
[rel]
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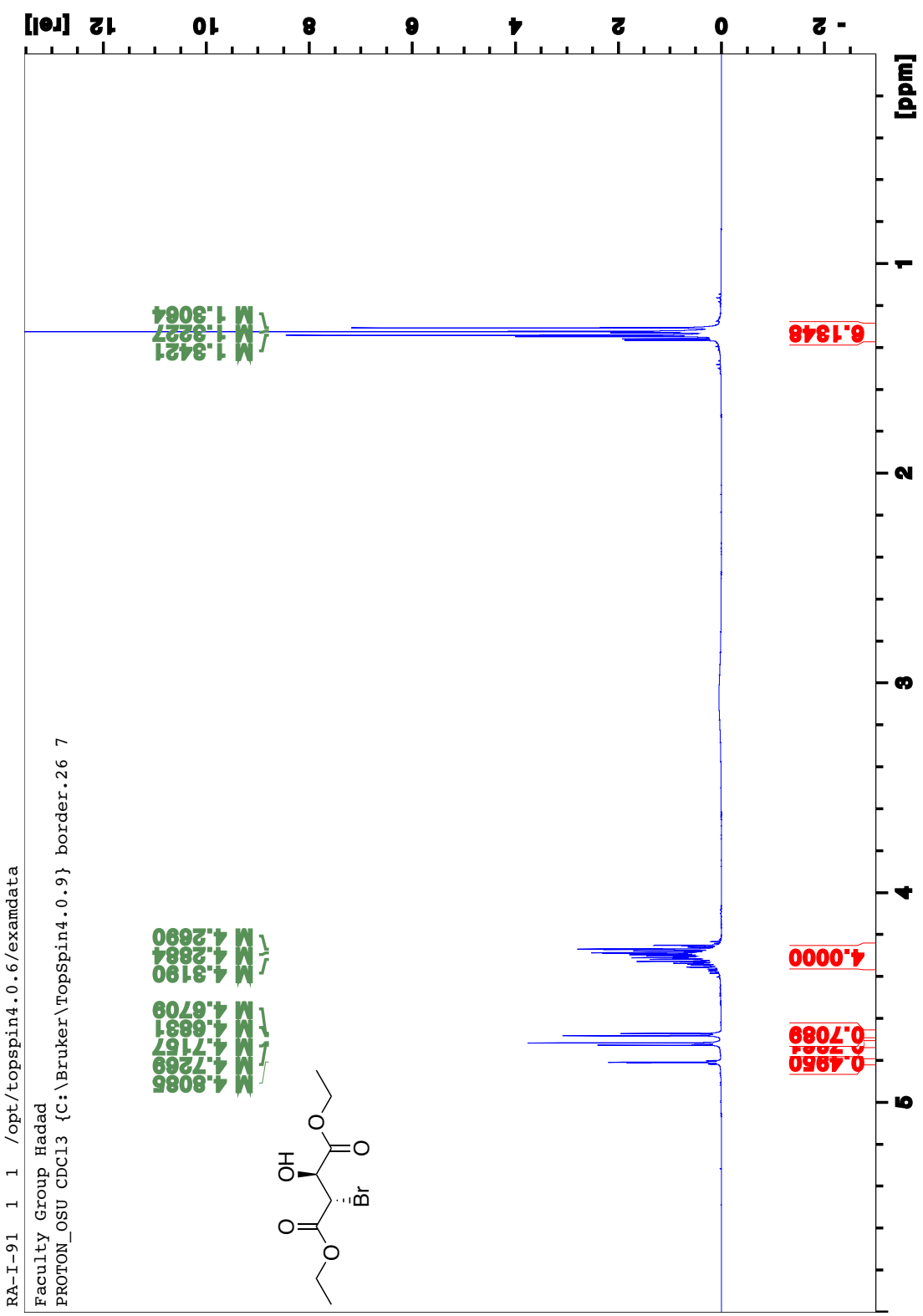
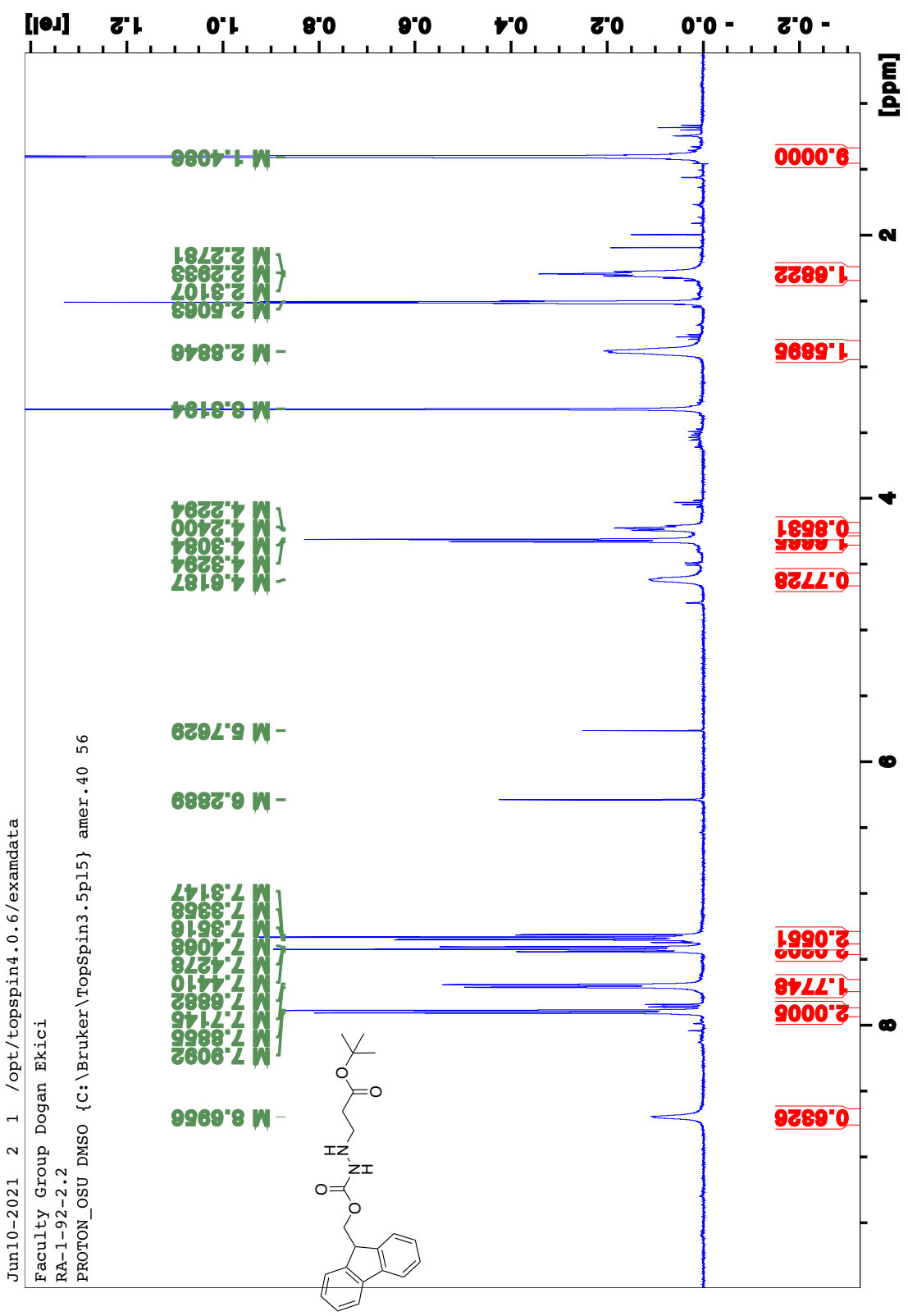
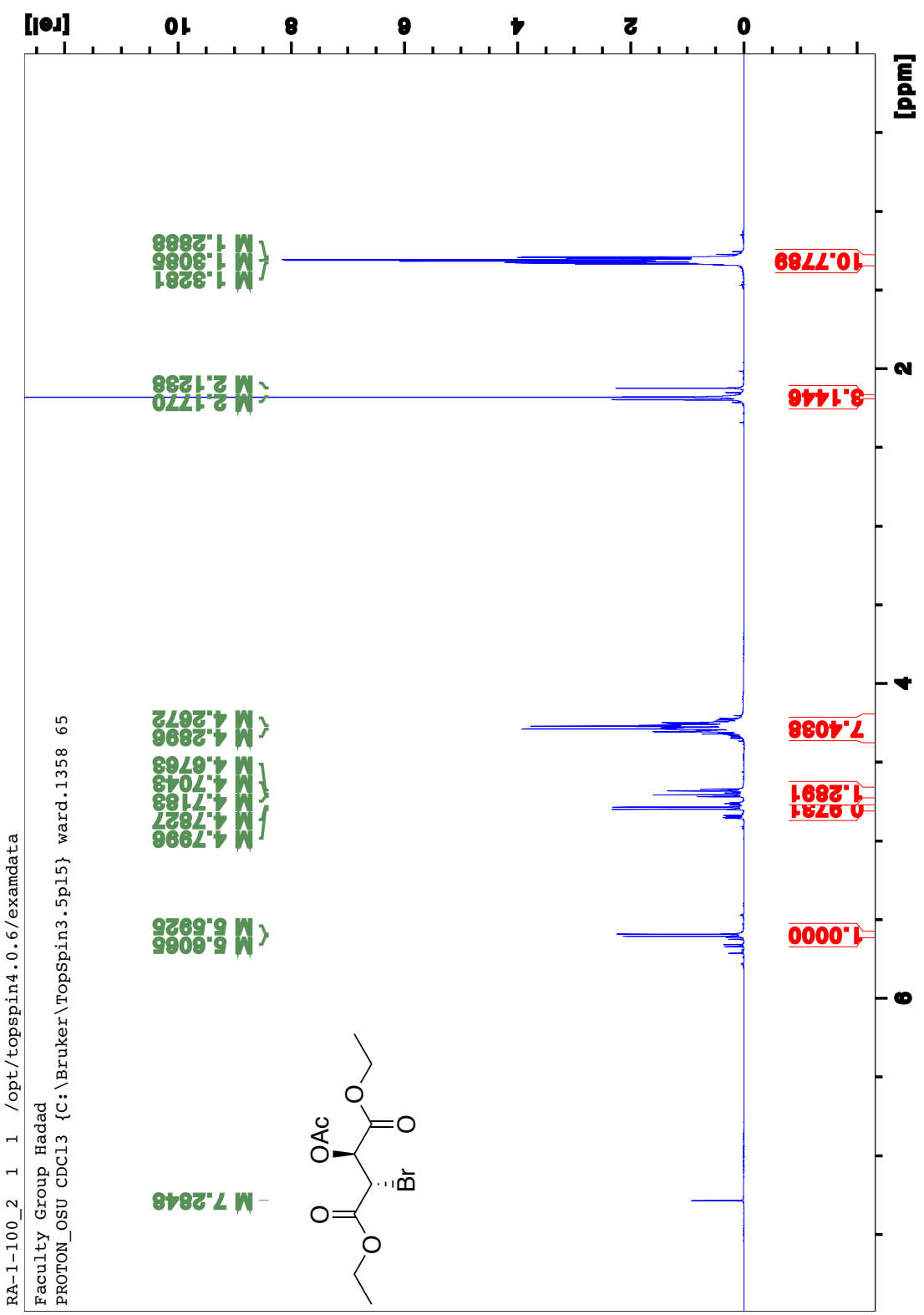
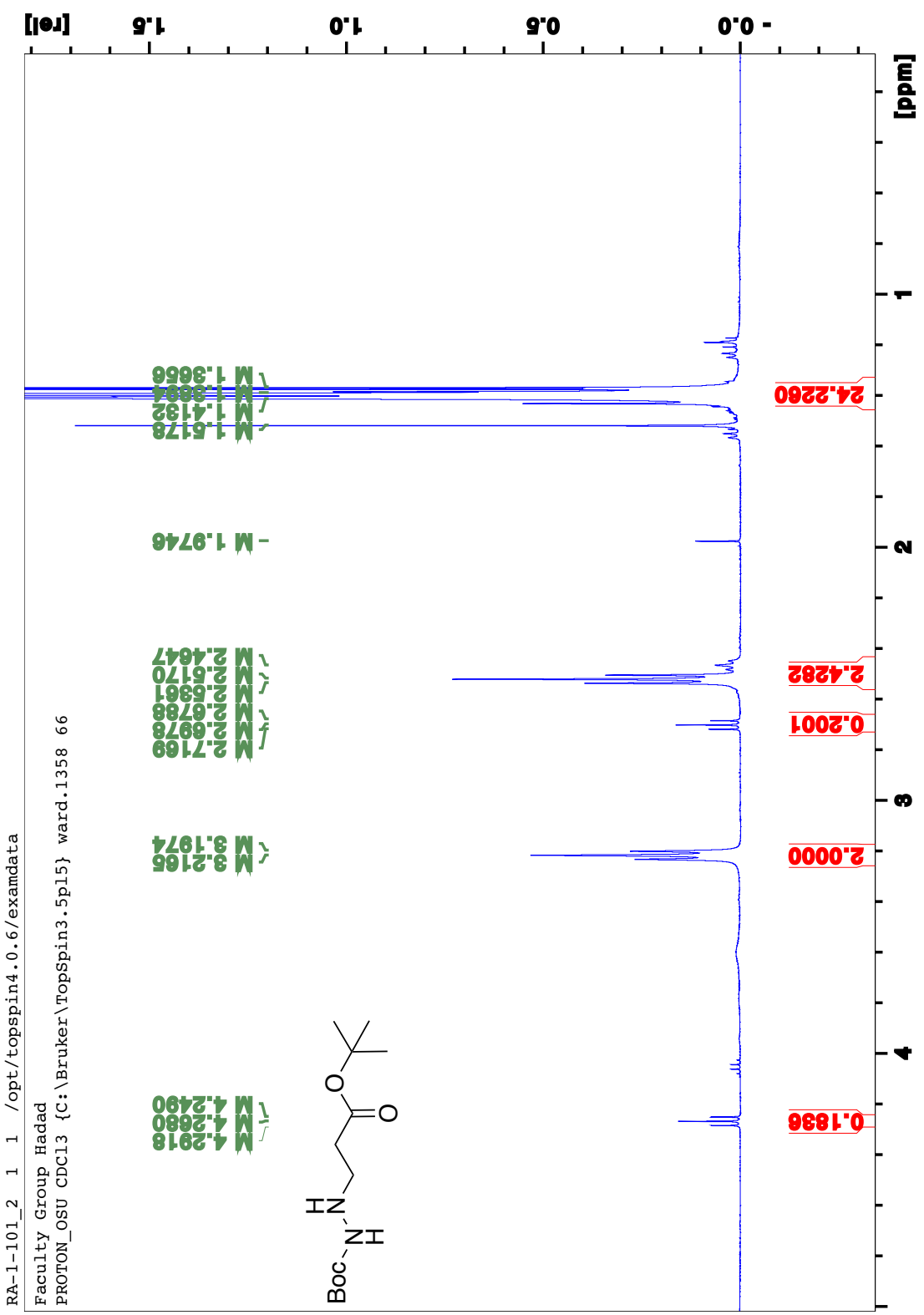
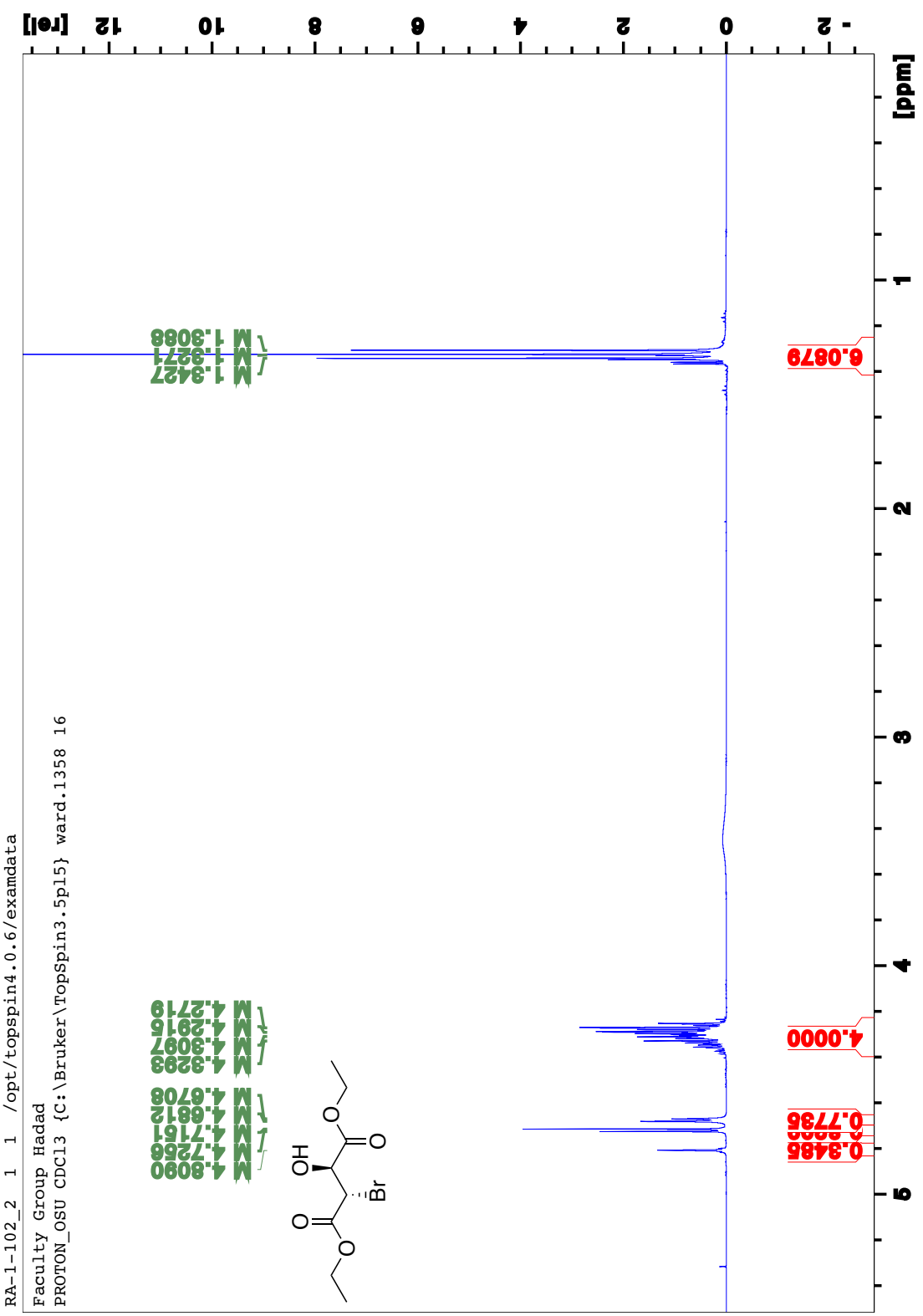
9.4433
2.0000
5.8864
2.8177
11.3586
7.9967
7.8816
7.3089
7.3433
6.0174
4.3562
4.2129
4.0403
2.8876
2.7289
2.4899
2.0823
1.8046
1.6120
1.4979
1.4248
0.8748
0.8486

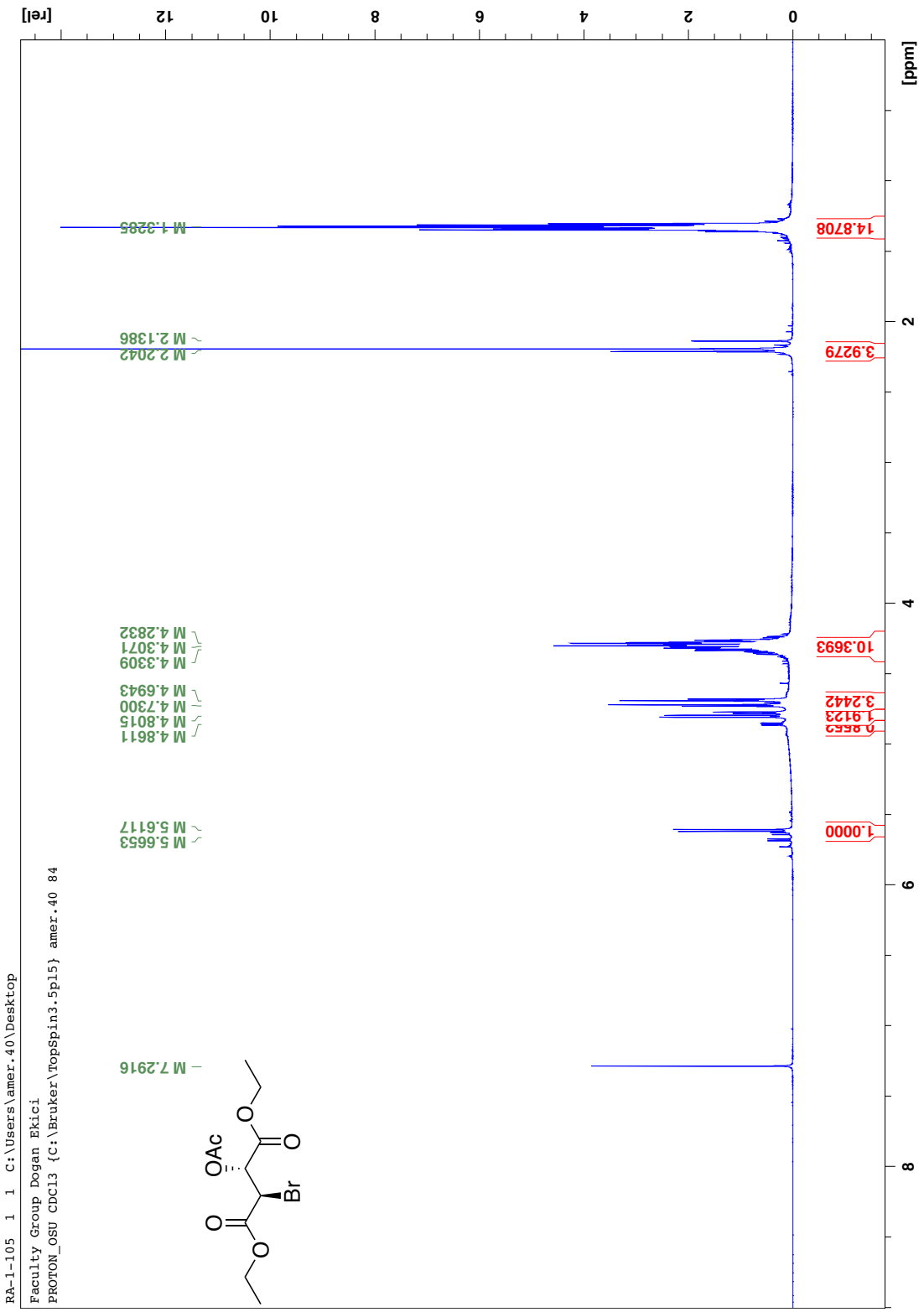

RA-I-91 1 1 /opt/topspin4.0.6/examdata
Faculty Group Hadad
PROTON_OSU CDCl3 {C:\Bruker\TopSpin4.0.9} border.26 7
[ppm]
[rel]
6.1348
4.0000
0.4850
0.7089
M 4.8086
M 4.7269
M 4.7167
M 4.6831
M 4.6709
M 4.3190
M 4.2884
M 4.2690
M 1.3421
M 1.3227
M 1.3064
OH
Br
O

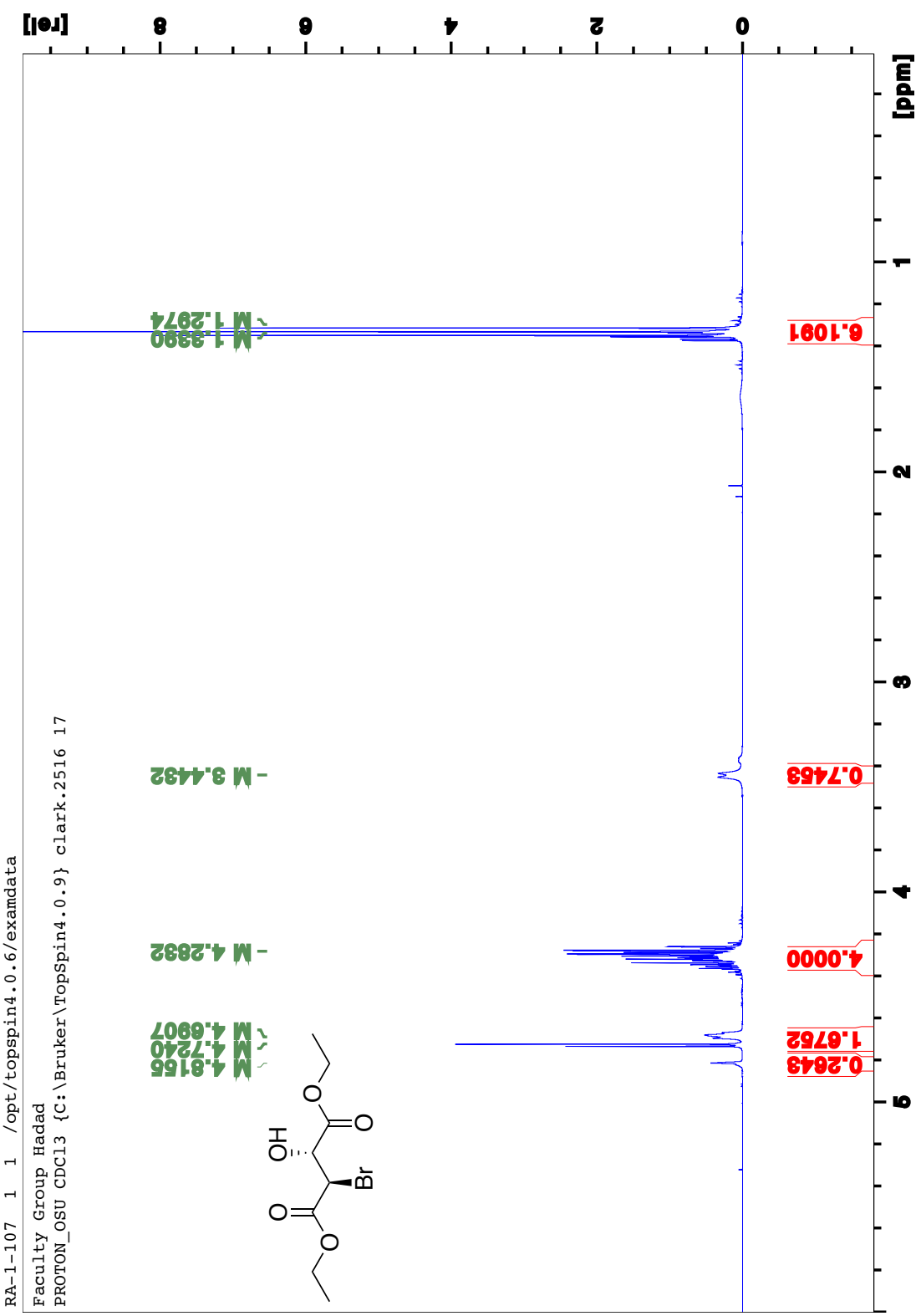

Jun10-2021 2 1 /opt/topspin4.0.6/examdata
Faculty Group Dogan Ekici
RA-1-92-2.2
PROTON_OSU DMSO {C:\Bruker\TopSpin3.5pl5} amer.40 56
[ppm]
[rel]
9.0000
2.0005
1.7748
2.0661
0.8326
1.6822
1.6896
0.7728
0.8531
M 1.4086
M 2.2781
M 2.2933
M 2.3107
M 2.5063
M 2.8846
M 3.3194
M 4.2294
M 4.2400
M 4.3084
M 4.3294
M 4.6187
M 5.7629
M 6.2889
M 7.3147
M 7.3368
M 7.3616
M 7.4068
M 7.4278
M 7.4410
M 7.6882
M 7.7146
M 7.8856
M 7.9092
M 8.6956

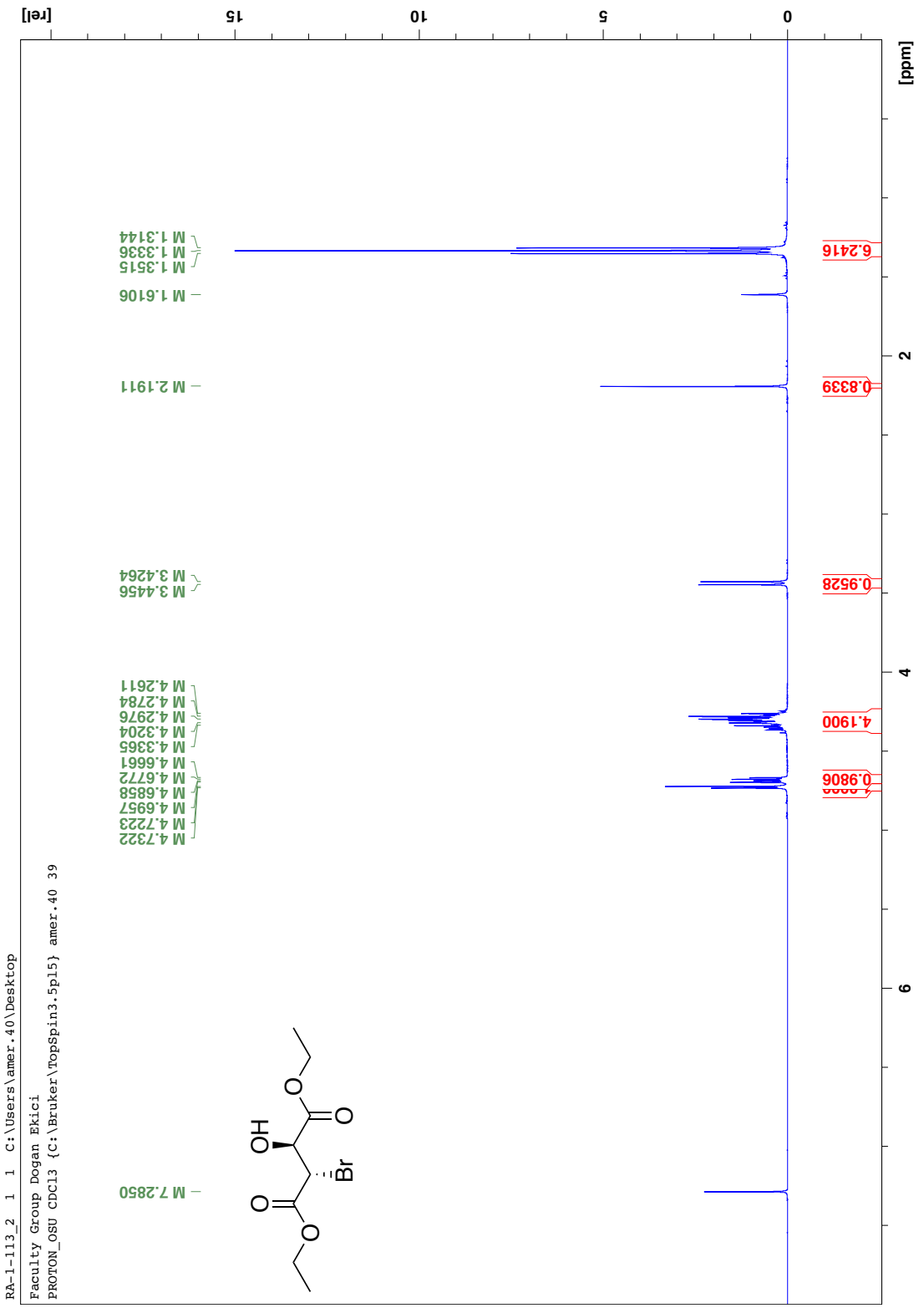

RA-1-100_2 1 1 /opt/topspin4.0.6/examdata
Faculty Group Hadad
PROTON_OSU CDCl3 {C:\Bruker\TopSpin3.5pl5} ward.1358 65
M 7.2848
M 6.6065
M 6.6925
M 4.7996
M 4.7827
M 4.7183
M 4.7043
M 4.6763
M 4.2896
M 4.2672
M 2.1770
M 2.1238
M 1.3281
M 1.3085
M 1.2888
OAc
Br
O
O
O
O
1.0000
0.9731
1.2891
7.4038
3.1446
10.7789
[ppm]
[rel]


RA-1-101_2 1 1 /opt/topspin4.0.6/examdata
Faculty Group Hadad
PROTON_OSU CDCl3 {C:\Bruker\TopSpin3.5pl5} ward.1358 66
M 4.2918
M 4.2680
M 4.2490
M 3.2165
M 3.1974
M 2.7169
M 2.6978
M 2.6788
M 2.5361
M 2.5170
M 2.4047
M 1.9746
M 1.6178
M 1.4182
M 1.3802
M 1.3656
0.1836
2.0000
0.2001
2.4282
24.2260
Boc
[ppm]
[rel]


RA-1-102_2 1 1 /opt/topspin4.0.6/examdata
Faculty Group Hadad
PROTON_OSU CDCl3 {C:\Bruker\TopSpin3.5pl5} ward.1358 16
[rel]
[ppm]
6.0879
4.0000
0.7736
0.3485
1.3427
1.3271
1.3088
4.8090
4.7266
4.7161
4.6812
4.6708
4.3293
4.3097
4.2916
4.2719
OH
Br
O


RA-1-105 1 1 C:\Users\amer.40\Desktop
Faculty Group Dogan Ekici
PROTON_OSU CDCl3 {C:\Bruker\TopSpin3.5p15} amer.40 84
M 7.2916
M 5.6653
M 5.6117
M 4.8611
M 4.8015
M 4.7300
M 4.6943
M 4.3309
M 4.3071
M 4.2832
M 2.2042
M 2.1386
M 1.3285
OAc
Br
O
O
O
O
1.0000
0.8653
1.9123
3.2442
10.3693
3.9279
14.8708
[rel]
[ppm]


RA-1-107 1 1 /opt/topspin4.0.6/examdata
Faculty Group Hadad
PROTON_OSU CDCl3 {C:\Bruker\TopSpin4.0.9} clark.2516 17
M 1.2974
M 1.3390
M 3.4432
M 4.2832
M 4.6907
M 4.7240
M 4.8165
6.1091
0.7453
4.0000
1.6752
0.2643
OH
Br
O
O
O
O
[ppm]
[rel]


RA-1-113_2 1 1 C:\Users\amer.40\Desktop
Faculty Group Dogan Ekici
PROTON_OSU CDCl3 {C:\Bruker\TopSpin3.5p15} amer.40 39
[rel]
15
10
5
0
[ppm]
6
4
2
M 7.2850
M 4.7322
M 4.7223
M 4.6957
M 4.6858
M 4.6772
M 4.6661
M 4.3365
M 4.3204
M 4.2976
M 4.2784
M 4.2611
M 3.4456
M 3.4264
M 2.1911
M 1.6106
M 1.3515
M 1.3336
M 1.3144
6.2416
0.8339
0.9528
4.1900
0.9806
OH
Br
O
O
O
O

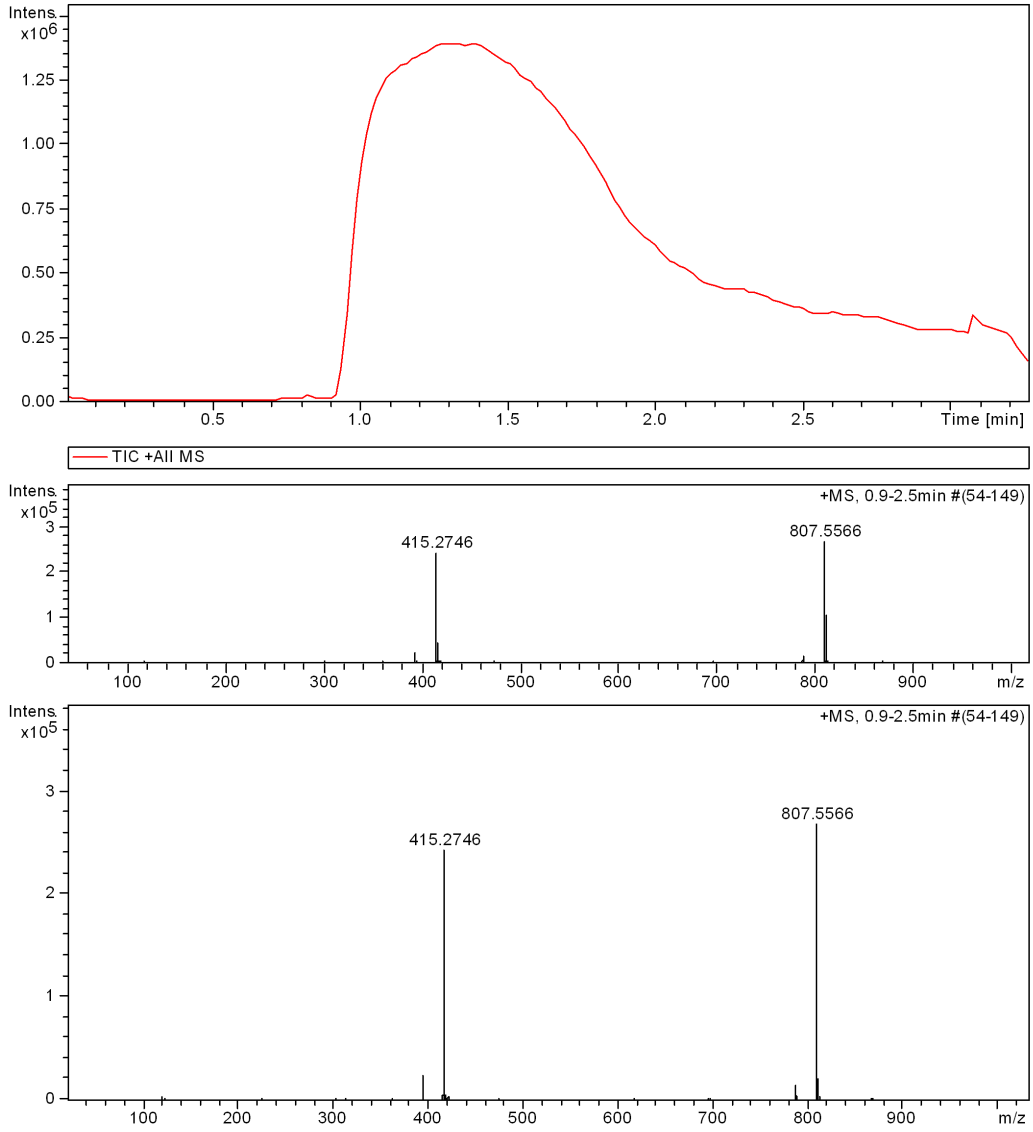
APPENDIX B

HRMS (ESI)

Generic Display Report

Analysis Info

Analysis Name	D:\Data\Dogan\amer\ESI test 2.d	Acquisition Date	5/16/2018 11:04:00 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA 1-4	Instrument	micrOTOF
Comment			



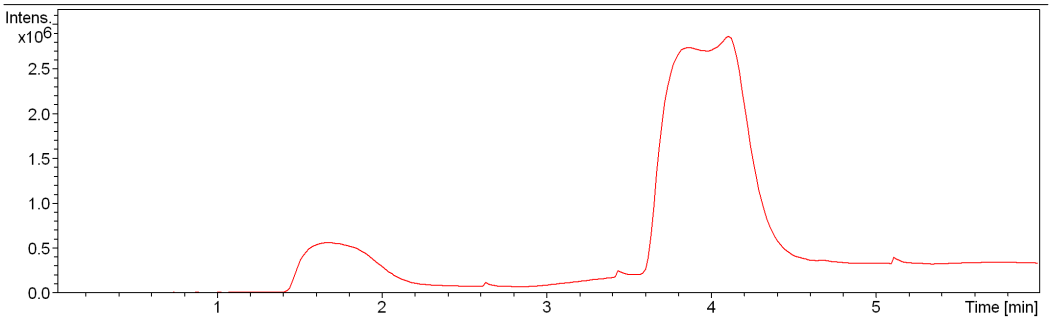
Display Report

Analysis Info

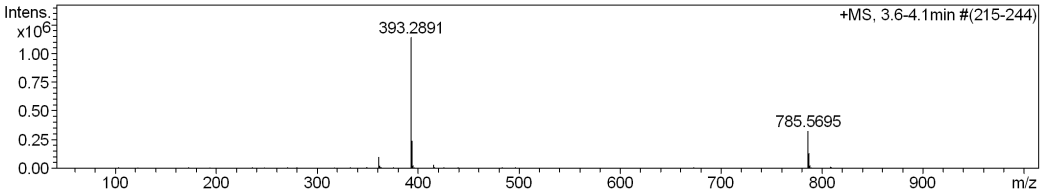
Analysis Name	D:\Data\Dogan\Kucway\RA-1-3.d	Acquisition Date	5/14/2018 10:48:28 AM
Method	Tune_Low.m	Operator	kucway.1
Sample Name	Z-Leu-leu-NHNH2	Instrument / Ser#	micrOTOF 194
Comment			

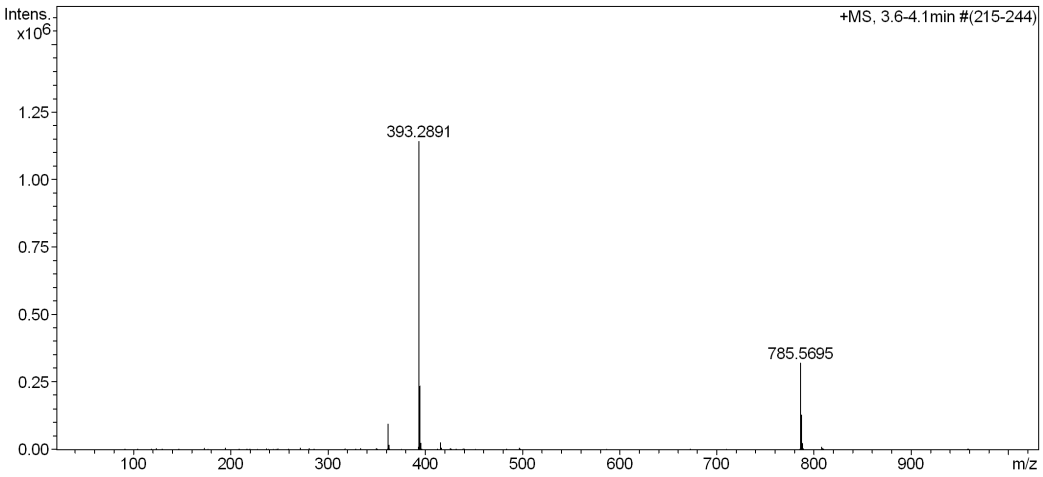
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



TIC +All MS





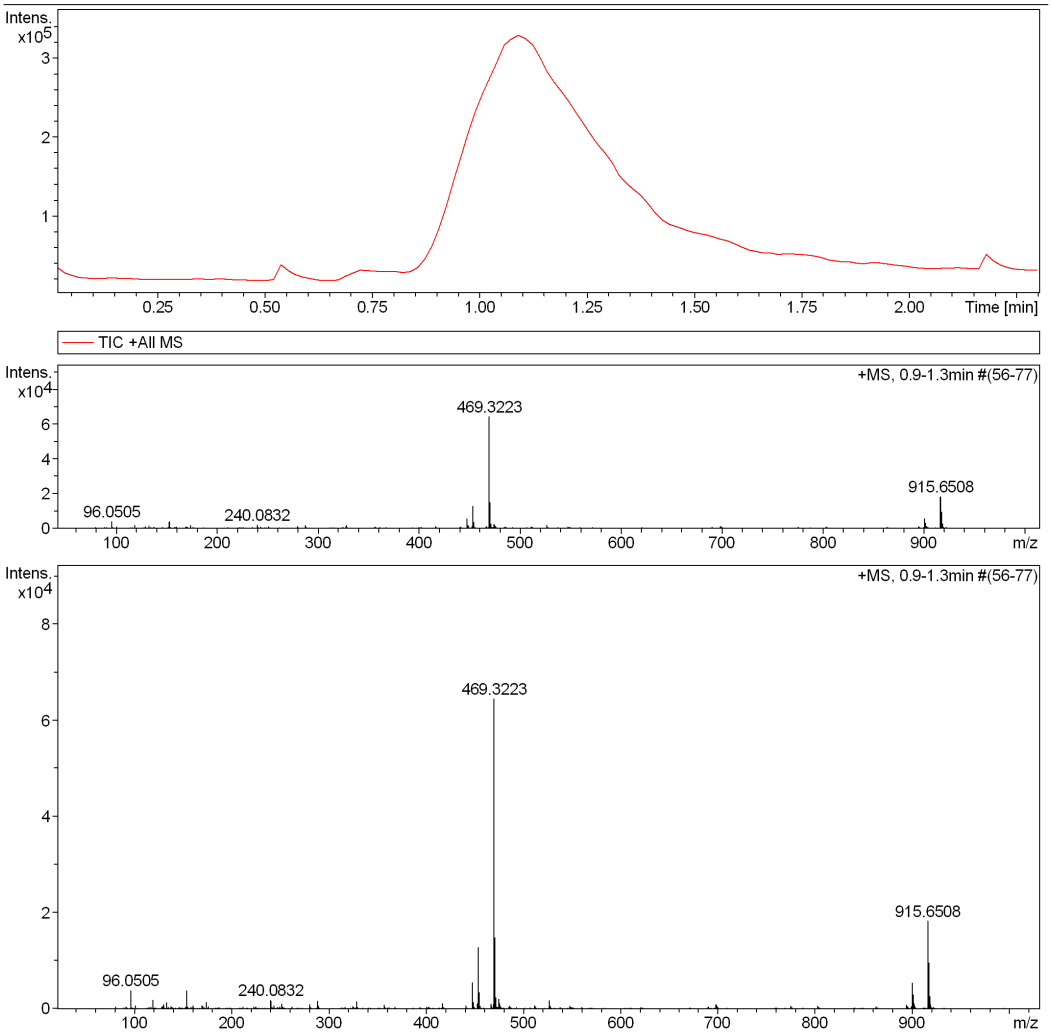
Display Report

Analysis Info

Analysis Name	D:\Data\Dogan\amer\RA-1 -5.d	Acquisition Date	5/17/2018 2:42:34 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA- 1-5	Instrument / Ser#	micrOTOF 194
Comment			

Acquisition Parameter

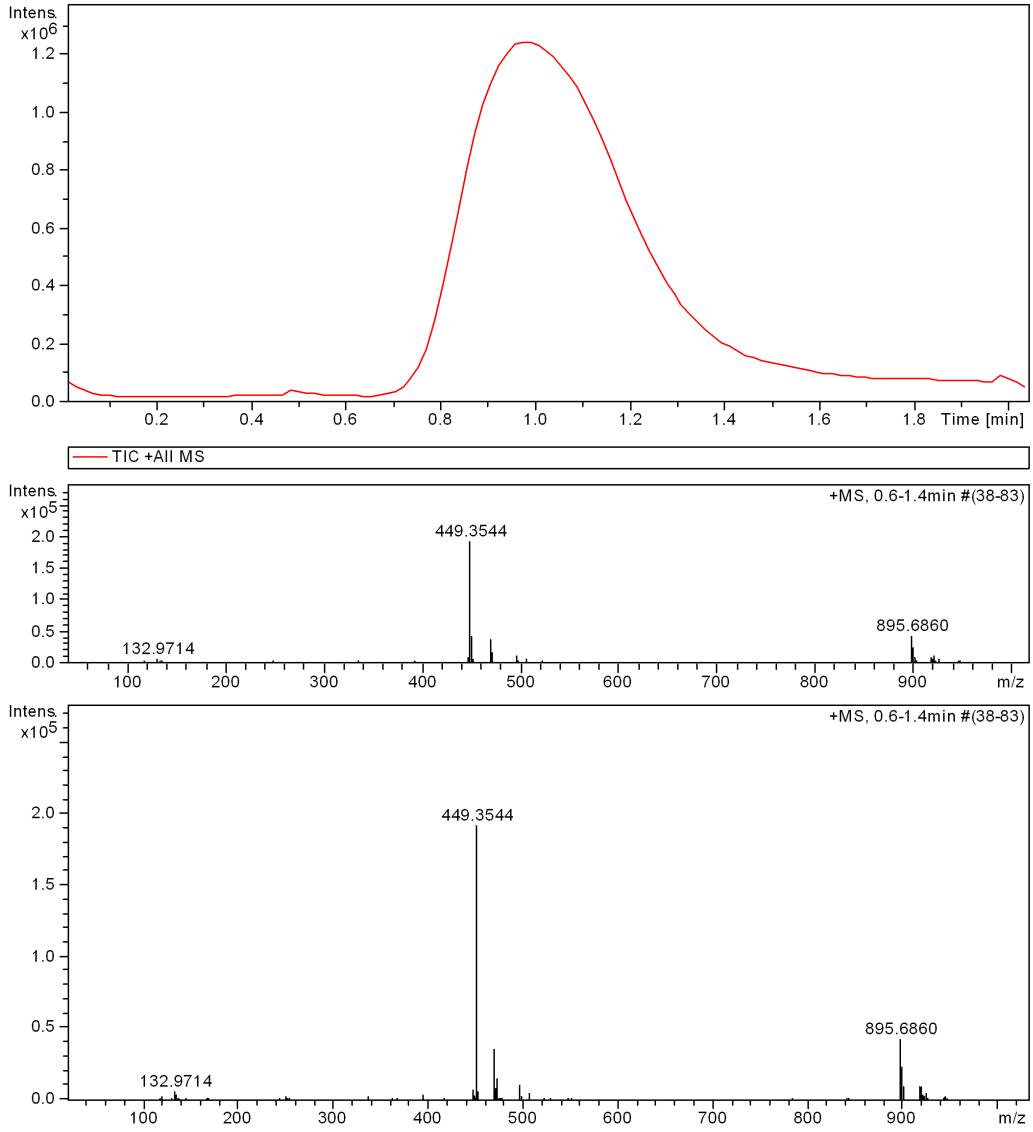
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



Generic Display Report

Analysis Info

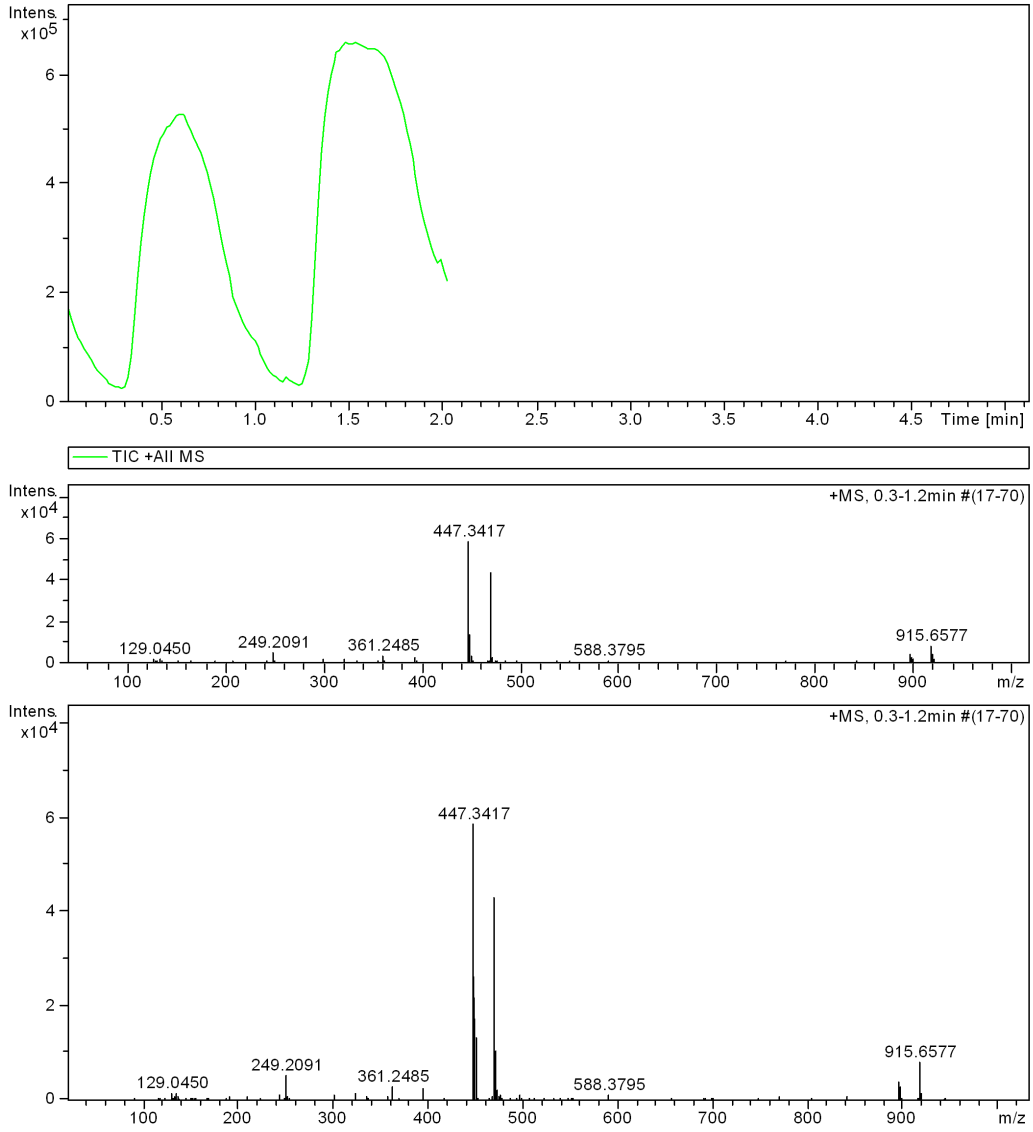
Analysis Name	D:\Data\Dogan\amer\RA-1-6-2.d	Acquisition Date	5/29/2018 10:33:51 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-6-2	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

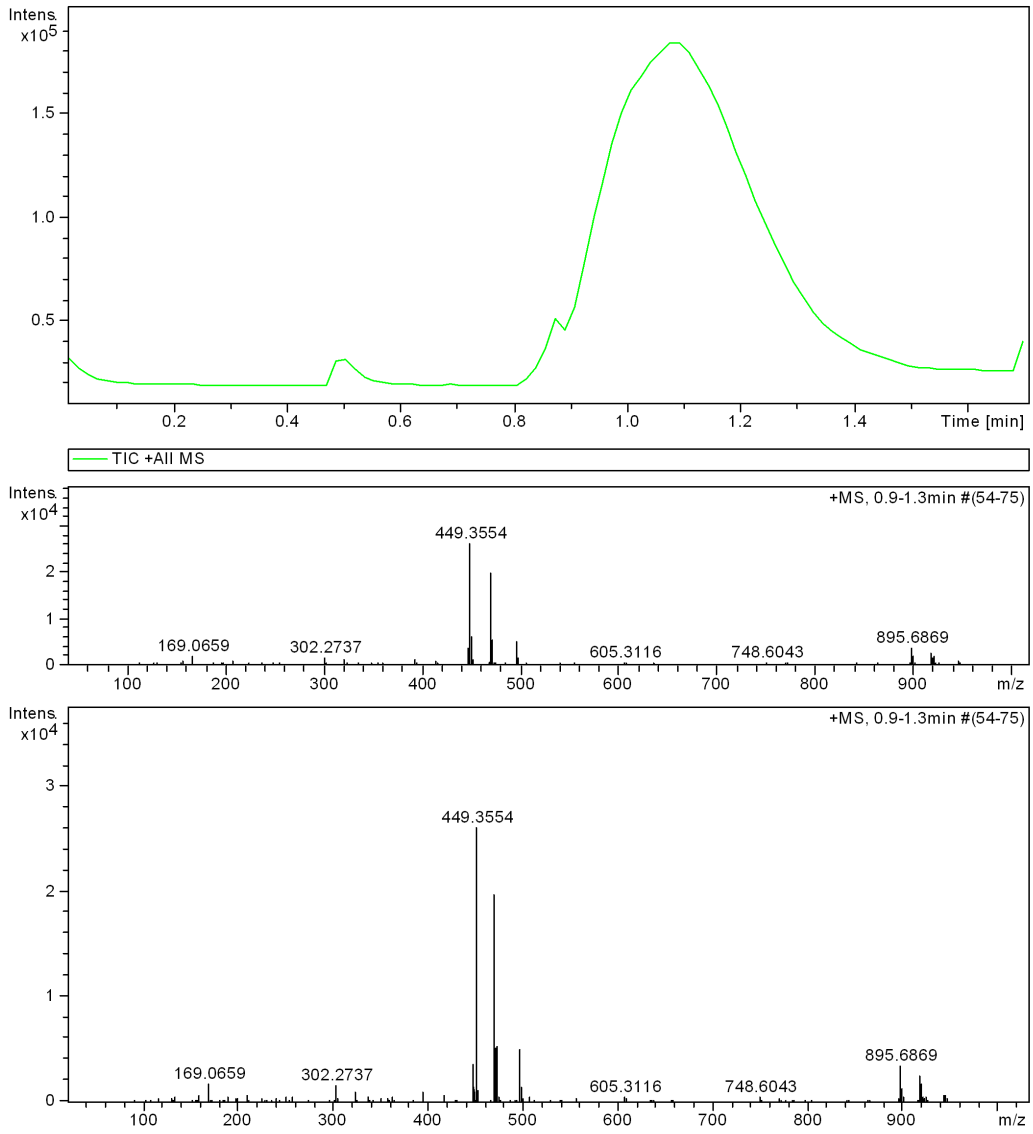
Analysis Name	D:\Data\Dogan\amer\RA-1-7.d	Acquisition Date	5/22/2018 2:56:40 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-7	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

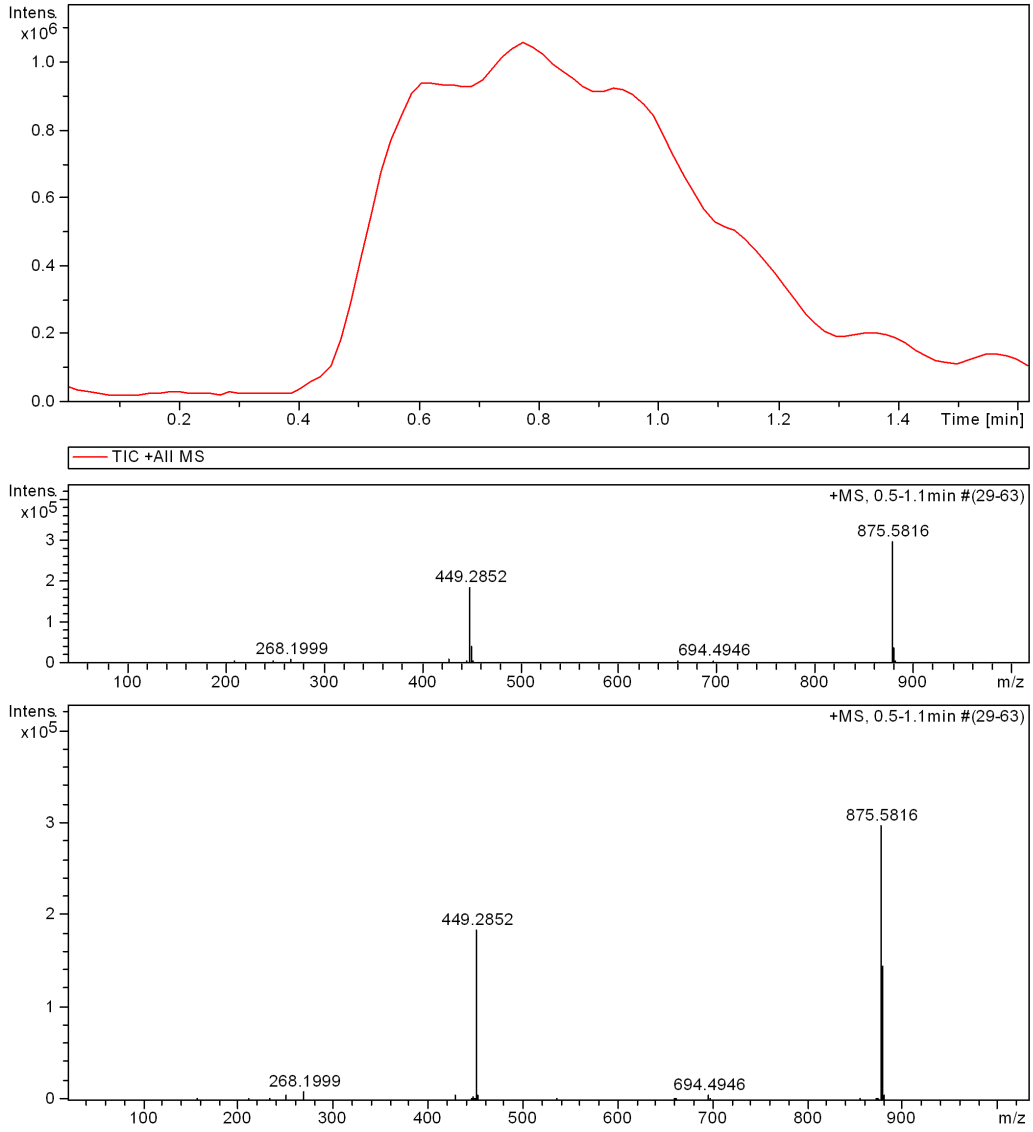
Analysis Name	D:\Data\Dogan\amer\RA-1-8-2.d	Acquisition Date	6/4/2018 11:22:25 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-8-2	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

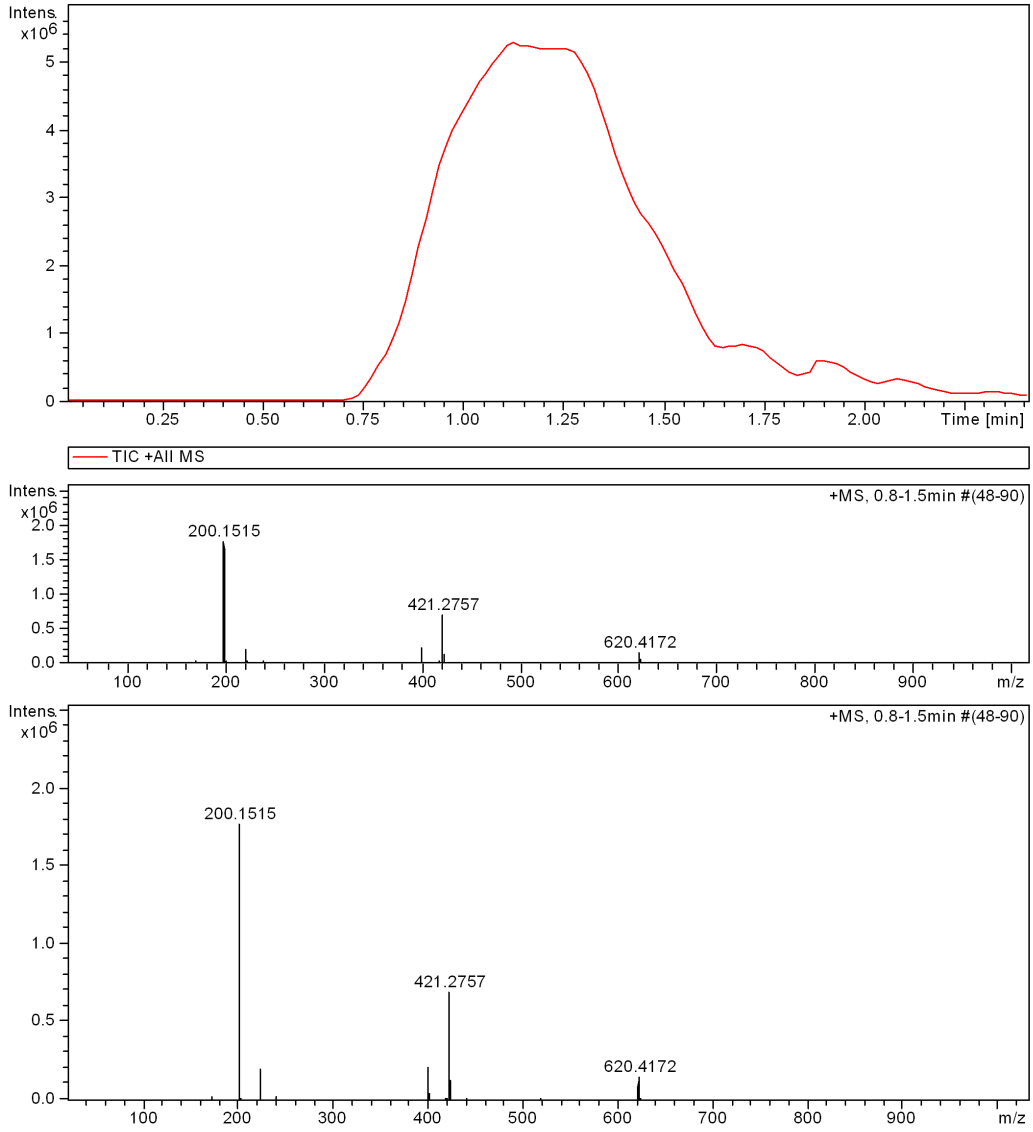
Analysis Name	D:\Data\Dogan\amer\RA-1-12-2.d	Acquisition Date	6/8/2018 10:11:42 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-12-2	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

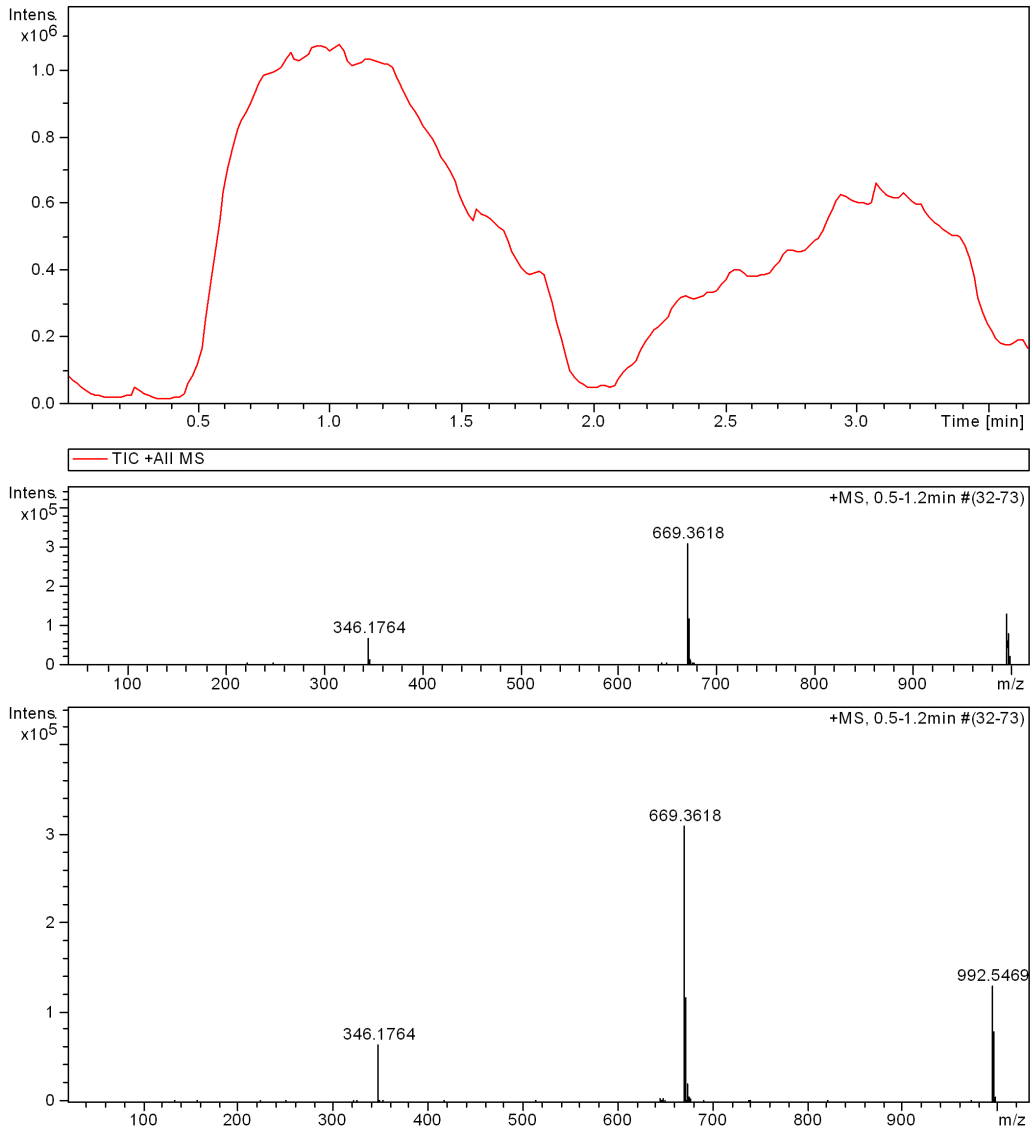
Analysis Name	D:\Data\Dogan\amer\RA-1-13.d	Acquisition Date	6/11/2018 4:12:07 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-13	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

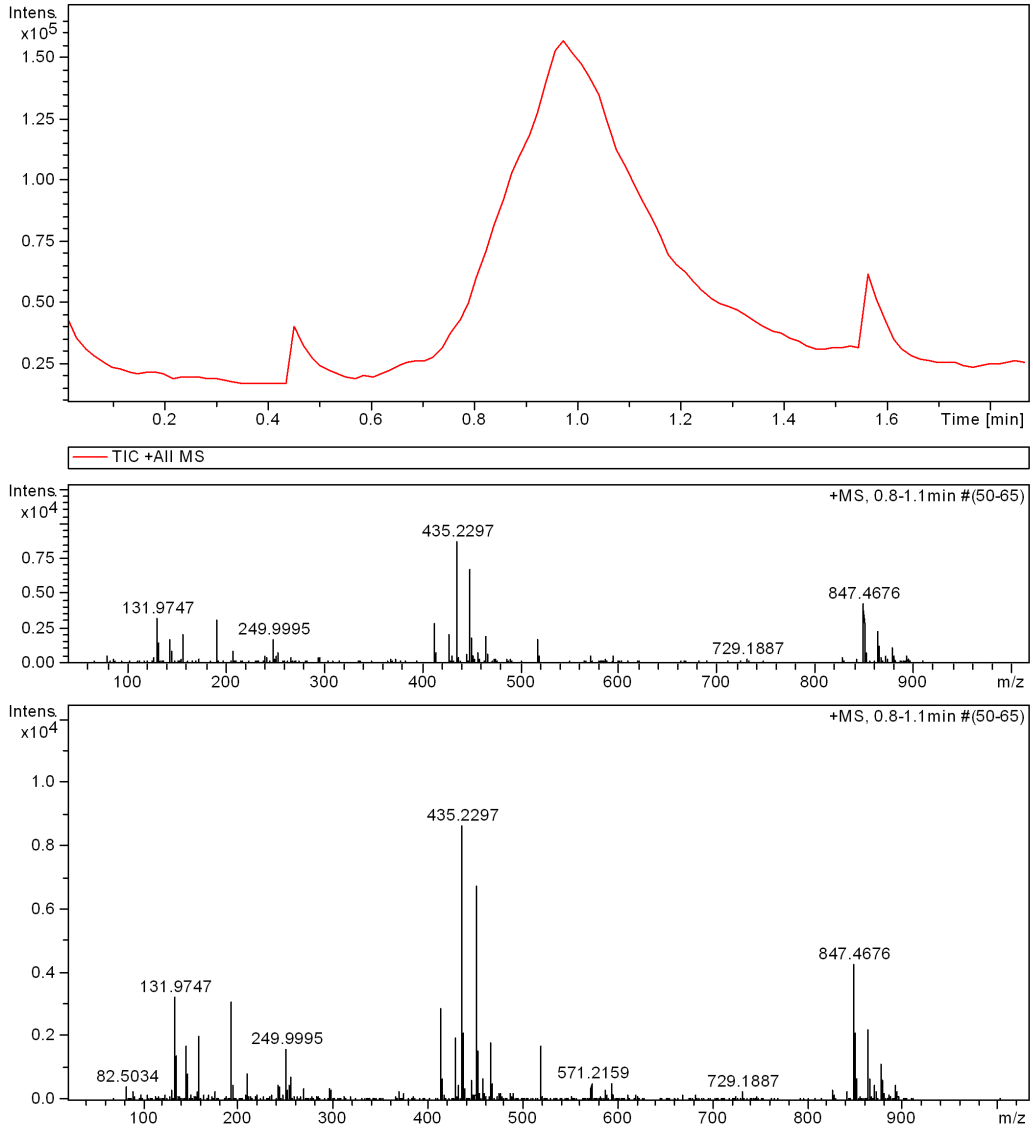
Analysis Name	D:\Data\Dogan\amer\RA-1-14.d	Acquisition Date	6/13/2018 1:07:11 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-14	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

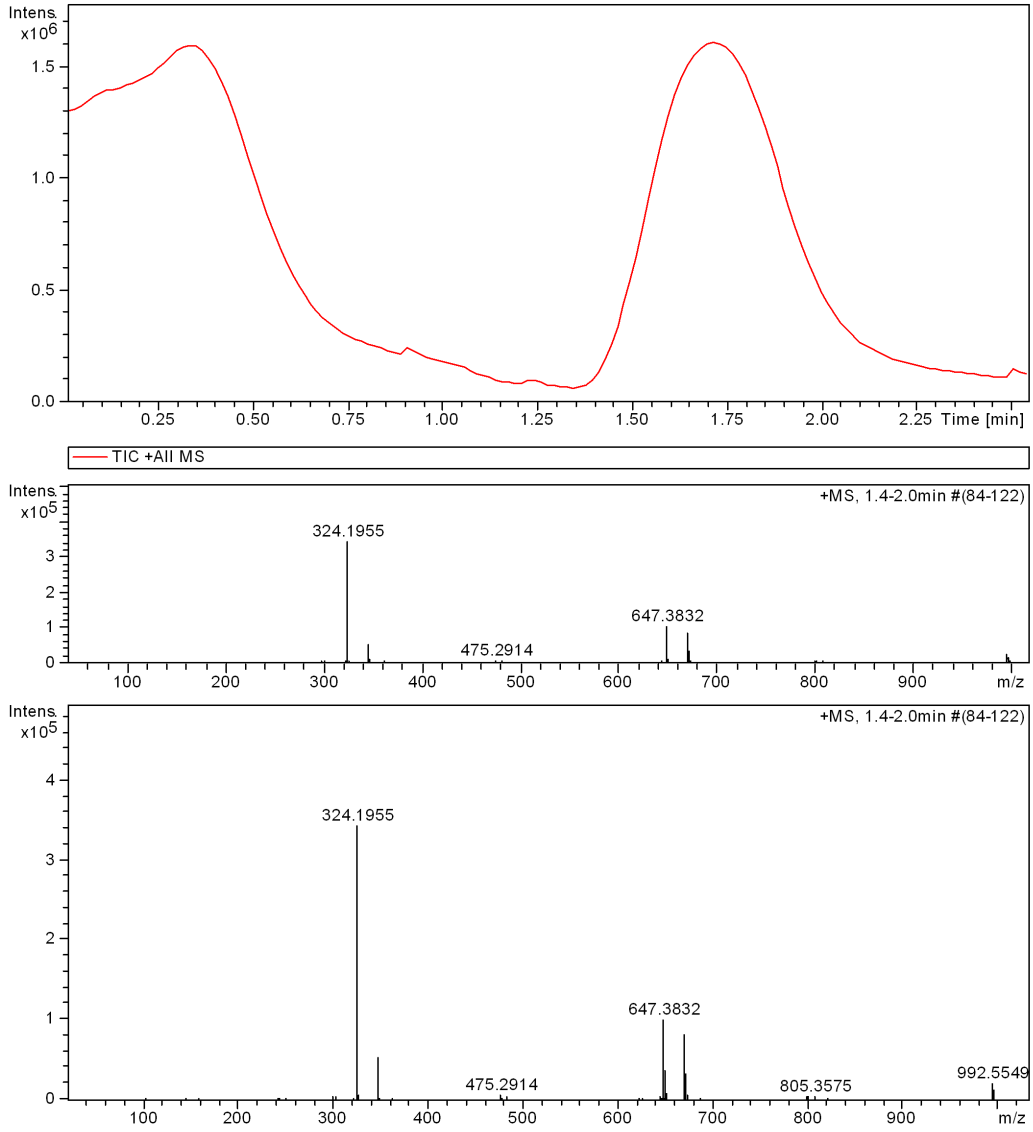
Analysis Name	D:\Data\Dogan\amer\RA-1-15-3.d	Acquisition Date	6/20/2018 11:23:25 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-15-2	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

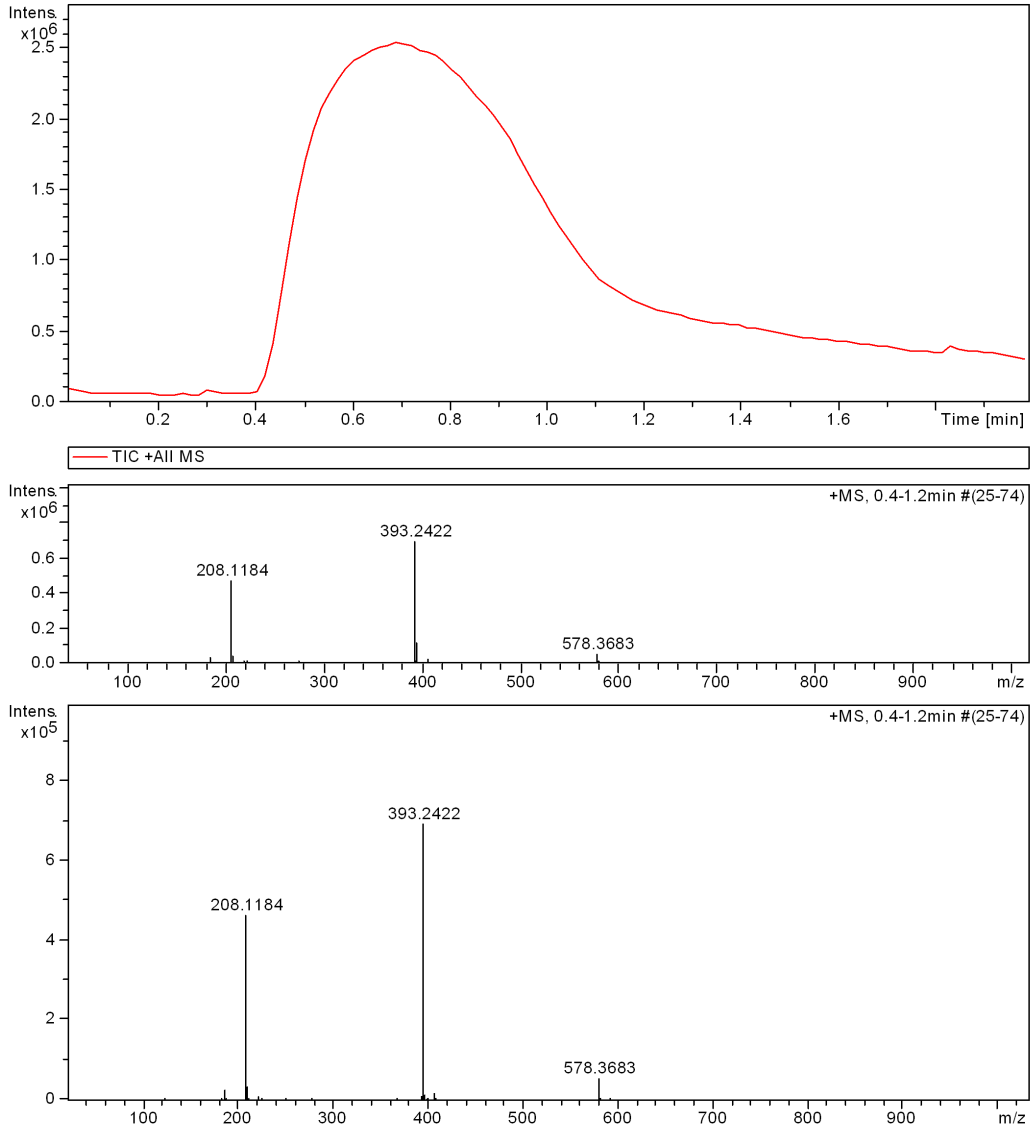
Analysis Name	D:\Data\Dogan\amer\RA-1-18.d	Acquisition Date	8/30/2018 1:07:50 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name	ra-1-18	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

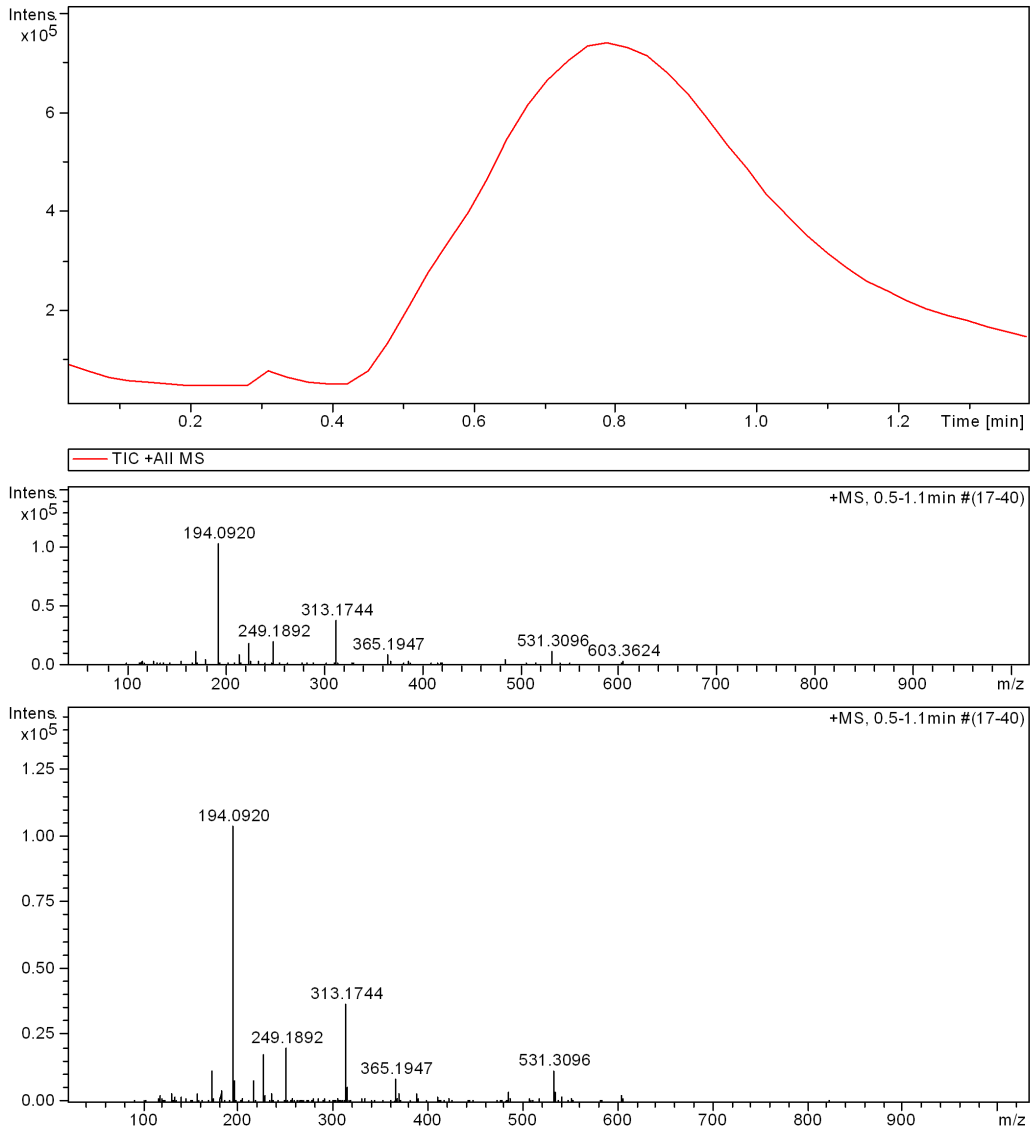
Analysis Name	D:\Data\Dogan\amer\RA-1-20.d	Acquisition Date	9/4/2018 10:38:44 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-20	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

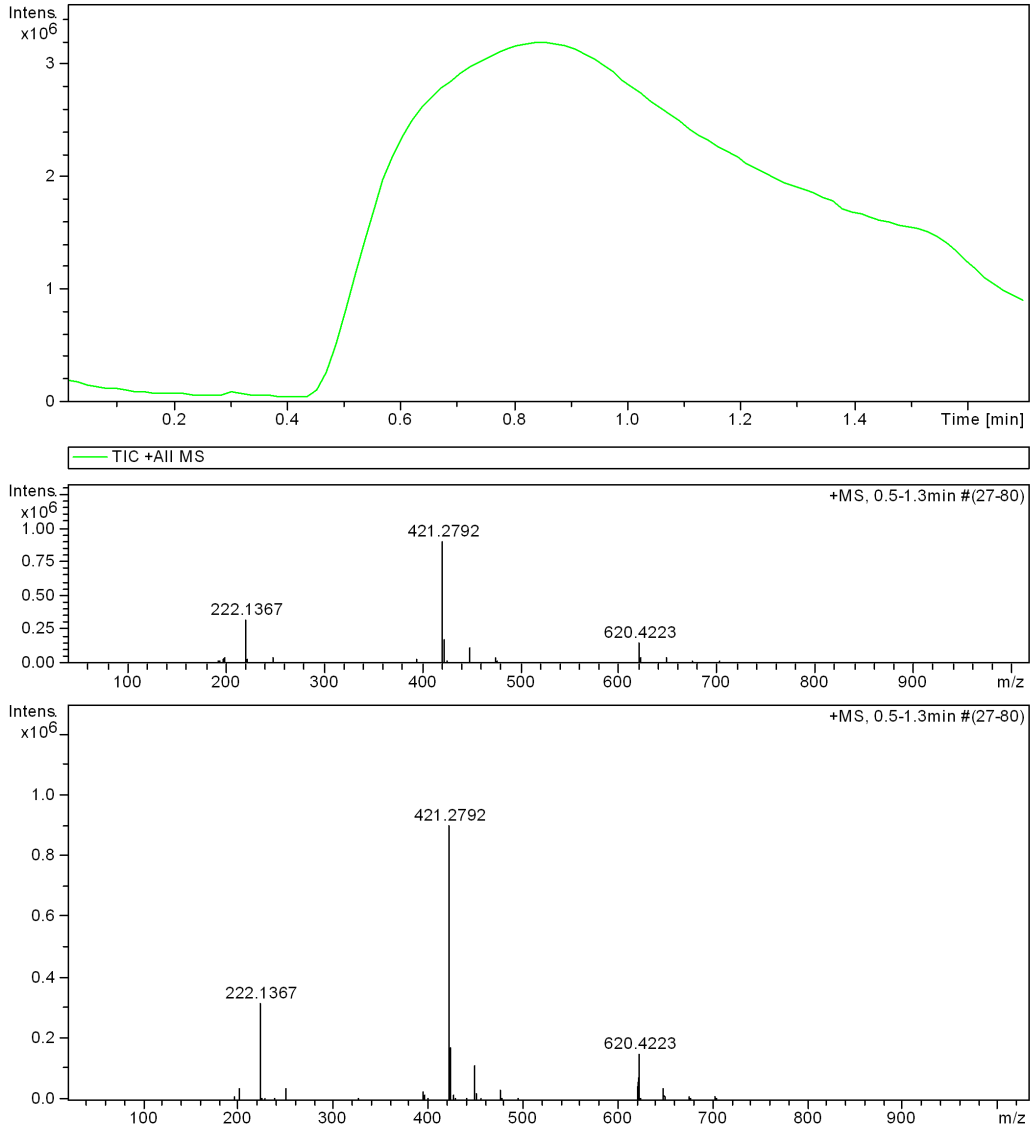
Analysis Name	D:\Data\Dogan\amer\RA-1-21.d	Acquisition Date	9/7/2018 12:03:21 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-21	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

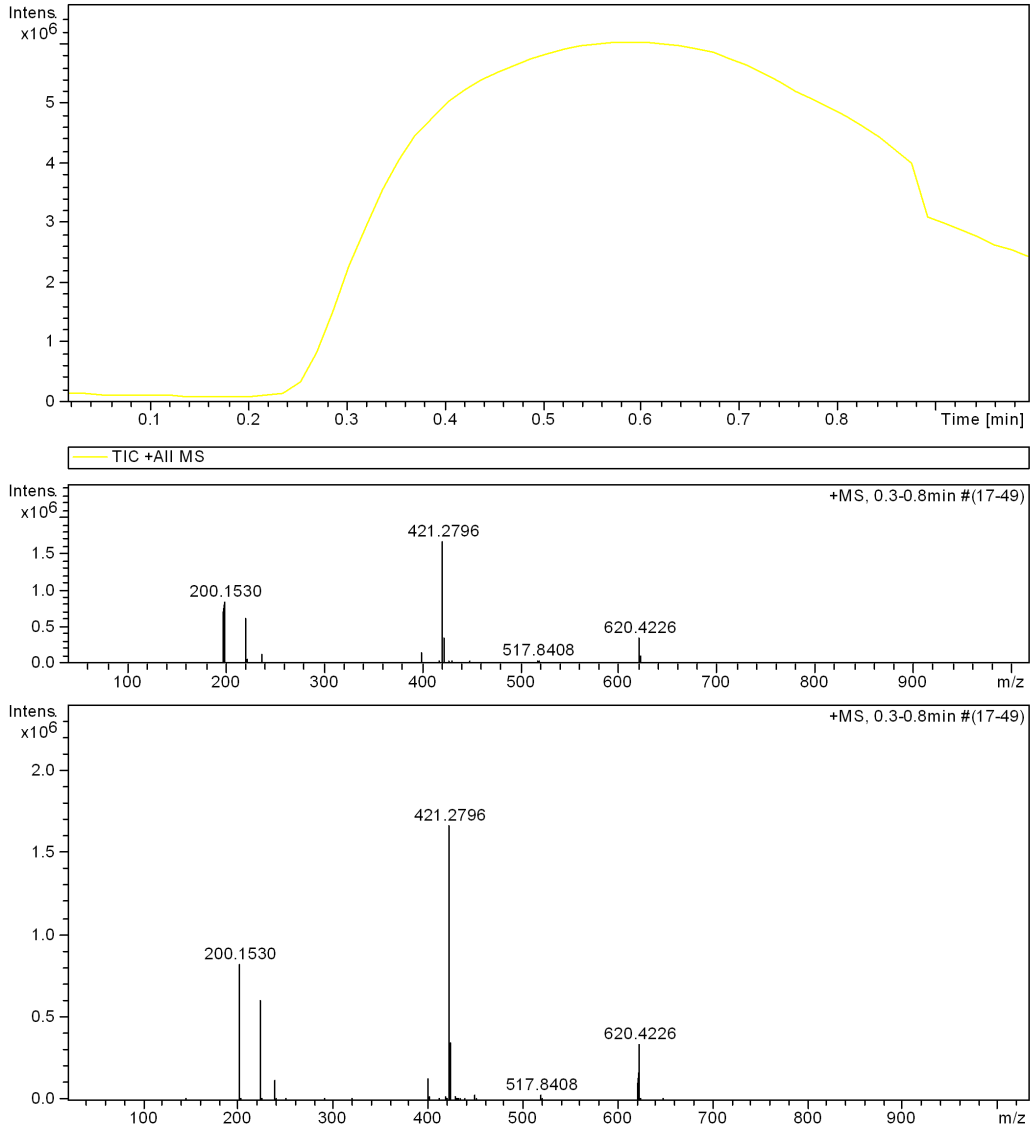
Analysis Name	D:\Data\Dogan\amer\RA-1-22.d	Acquisition Date	9/12/2018 11:16:53 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-22	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

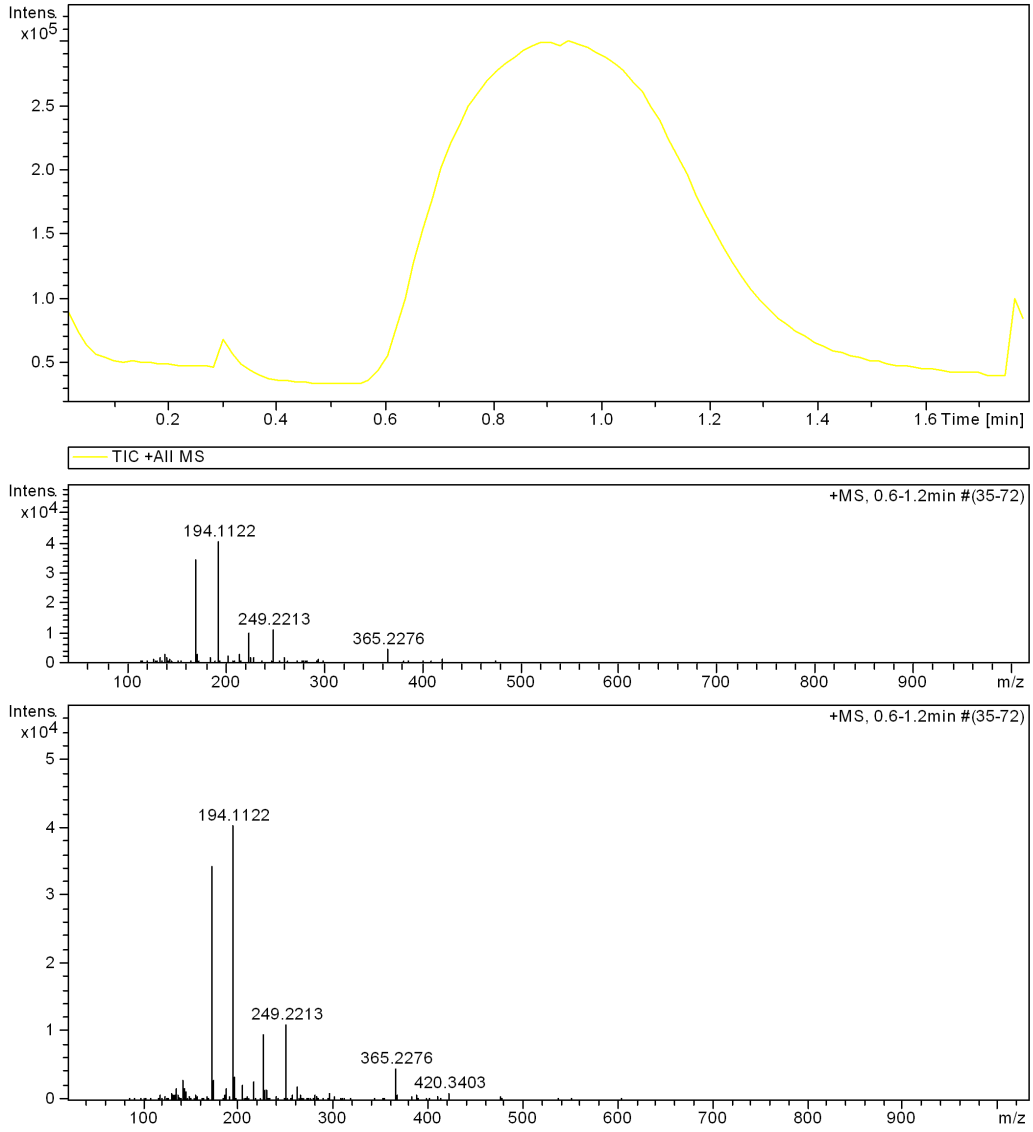
Analysis Name	D:\Data\Dogan\amer\RA-1-23.d	Acquisition Date	9/12/2018 11:27:13 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-23	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

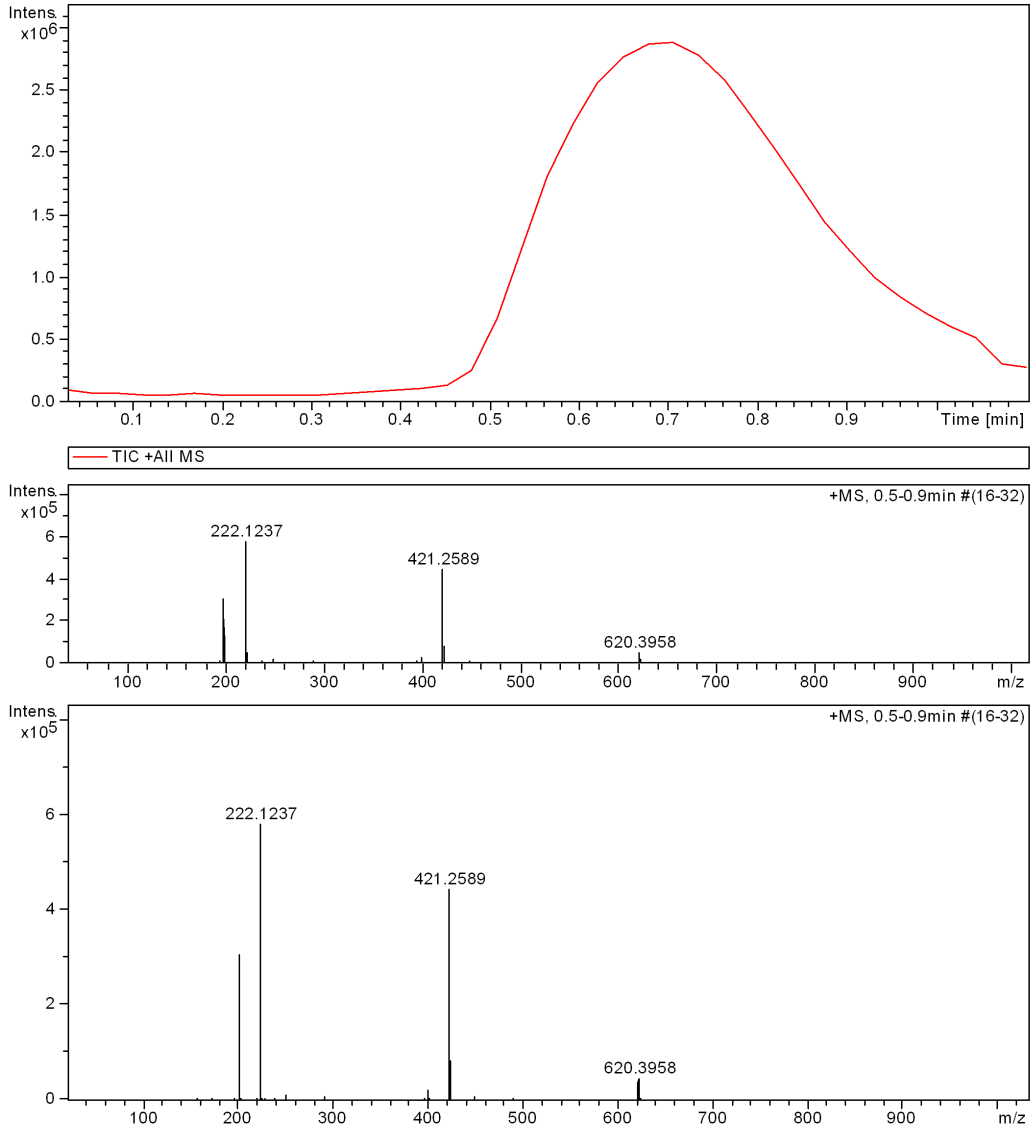
Analysis Name	D:\Data\Dogan\amer\RA-1-24-3.d	Acquisition Date	9/24/2018 9:15:07 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-24-3	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

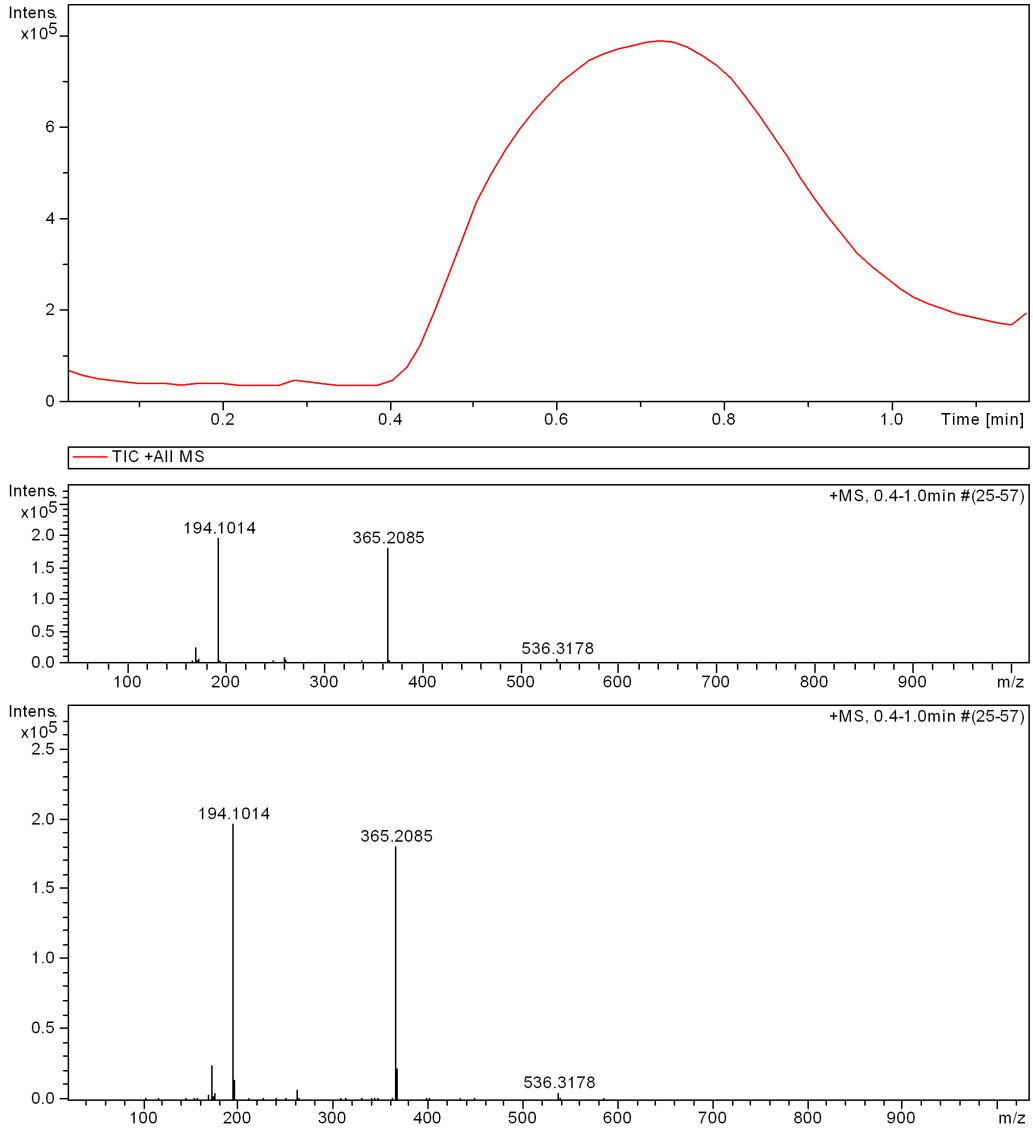
Analysis Name	D:\Data\Dogan\amer\RA-1-25.d	Acquisition Date	9/19/2018 11:41:53 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name	RA-1-25	Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

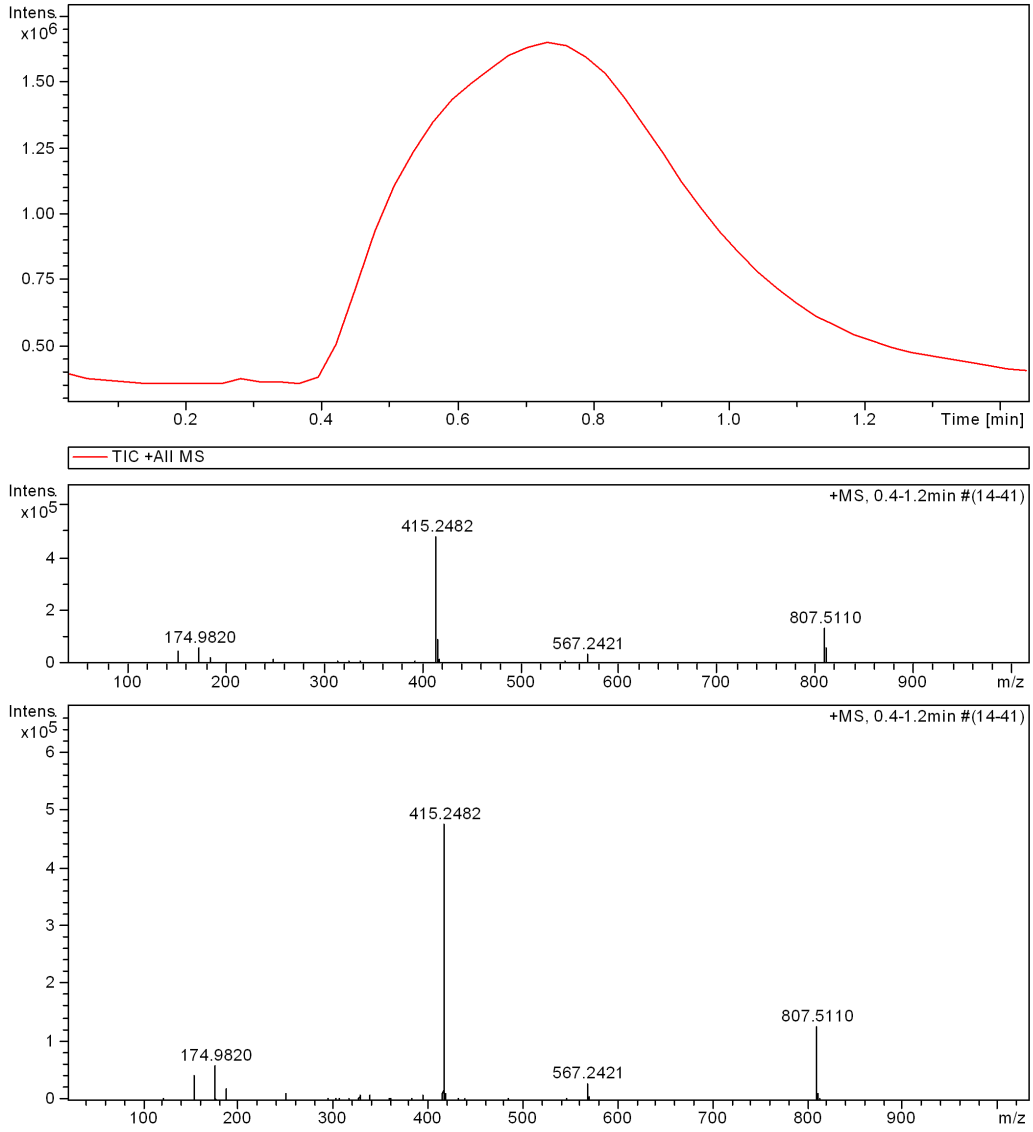
Analysis Name	D:\Data\Dogan\amer\RA-1-28.d	Acquisition Date	10/4/2018 9:12:41 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

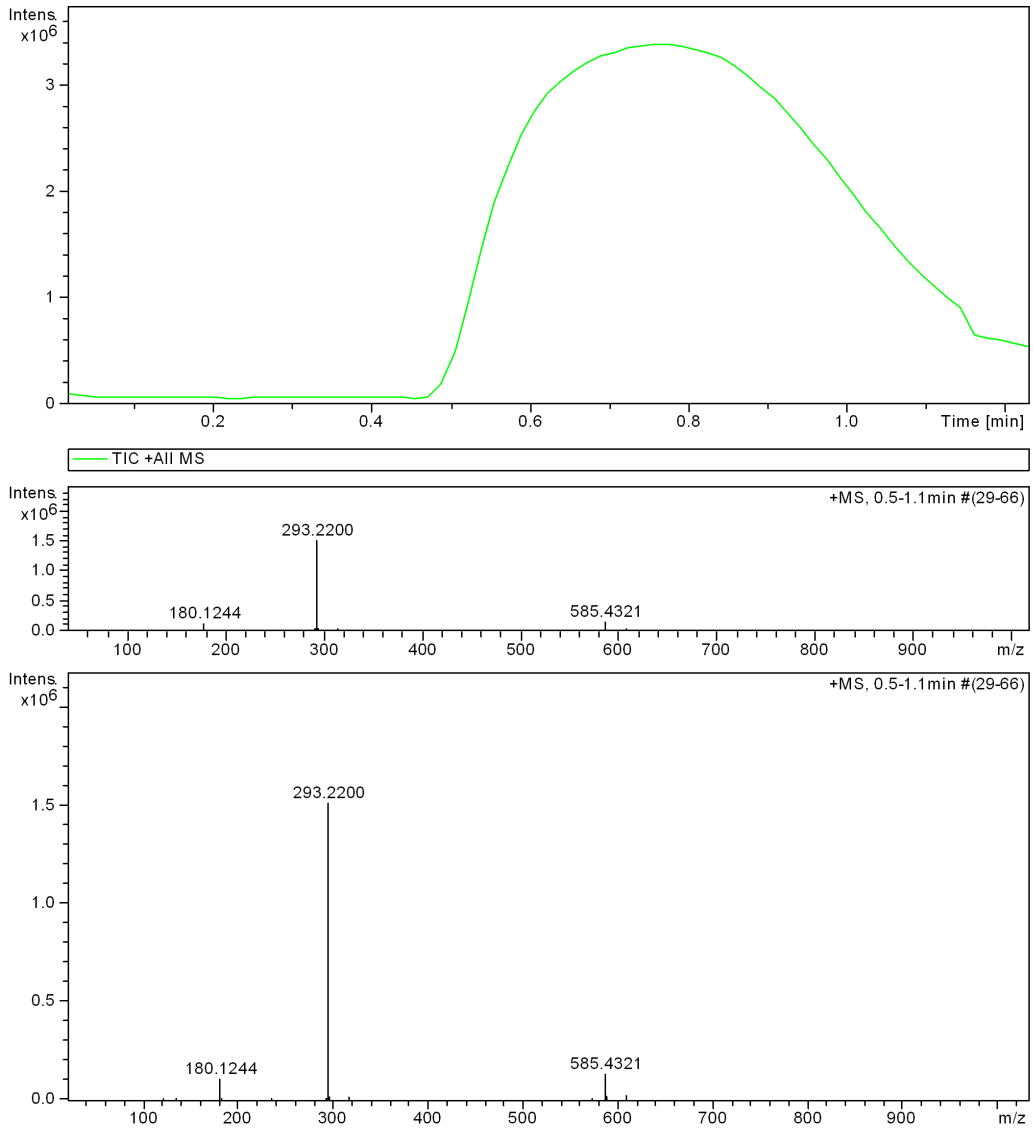
Analysis Name	D:\Data\Dogan\amer\RA-1-29.d	Acquisition Date	10/3/2018 10:34:20 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

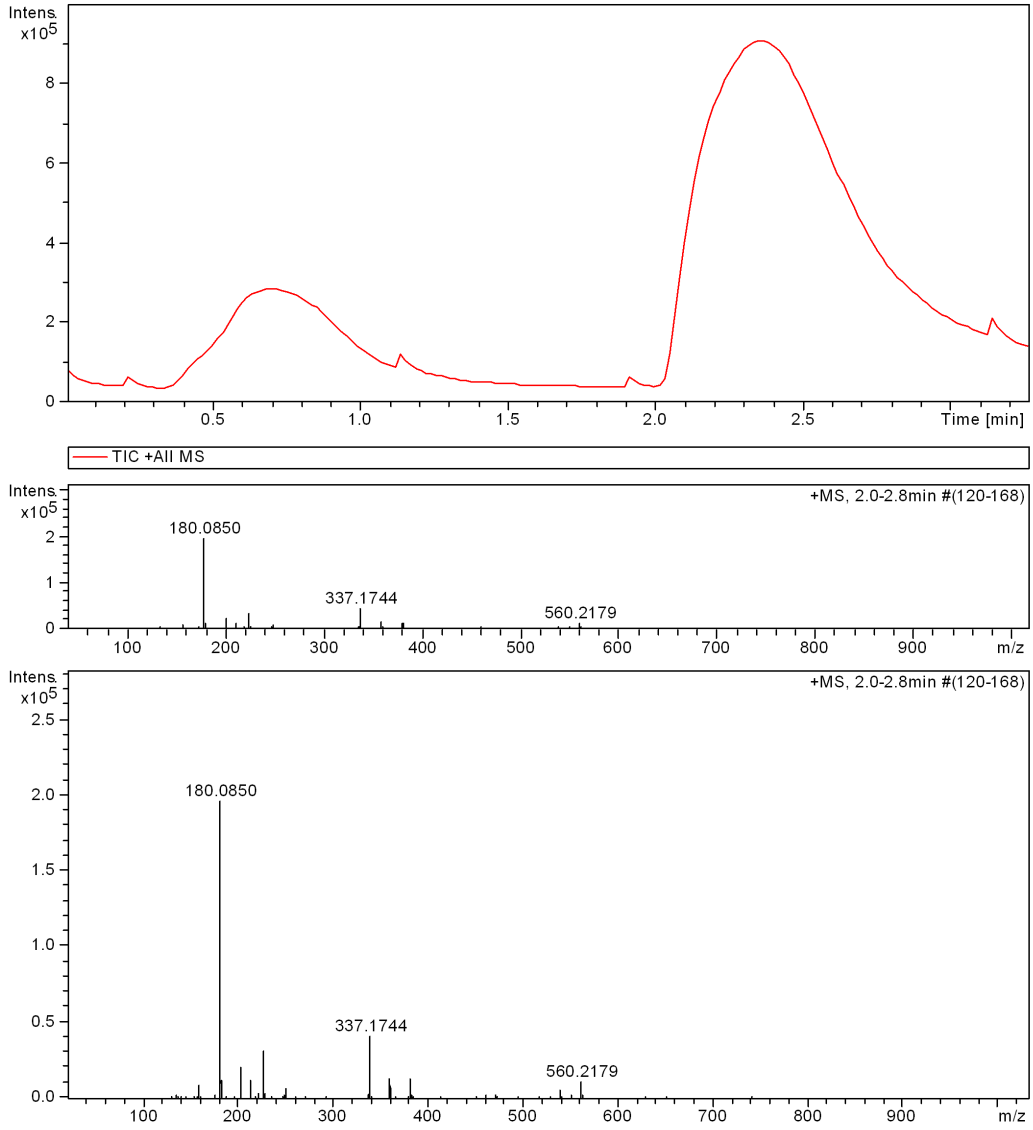
Analysis Name	D:\Data\Dogan\amer\RA-1-30.d	Acquisition Date	10/4/2018 9:18:56 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

Analysis Name	D:\Data\Dogan\amer\RA-1-31.d	Acquisition Date	10/9/2018 4:25:16 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



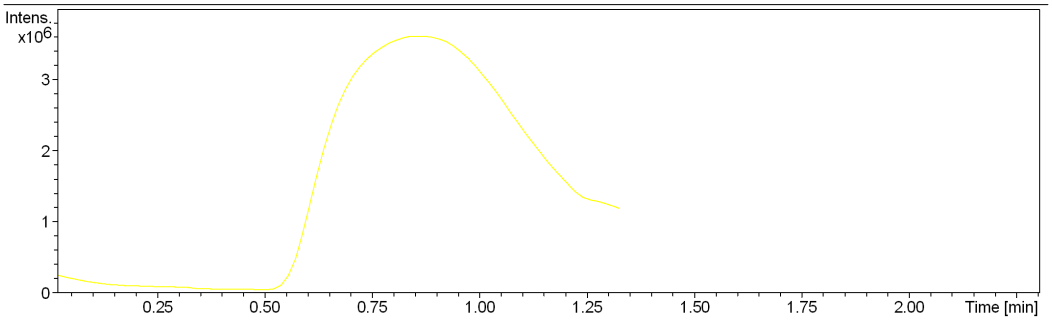
Display Report

Analysis Info

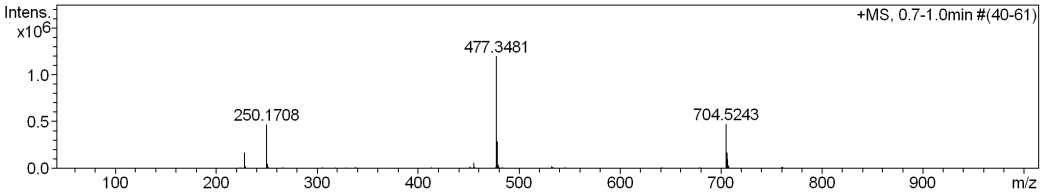
Analysis Name	D:\Data\Dogan\amer\RA-1-32-2.d	Acquisition Date	10/17/2018 12:00:41 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

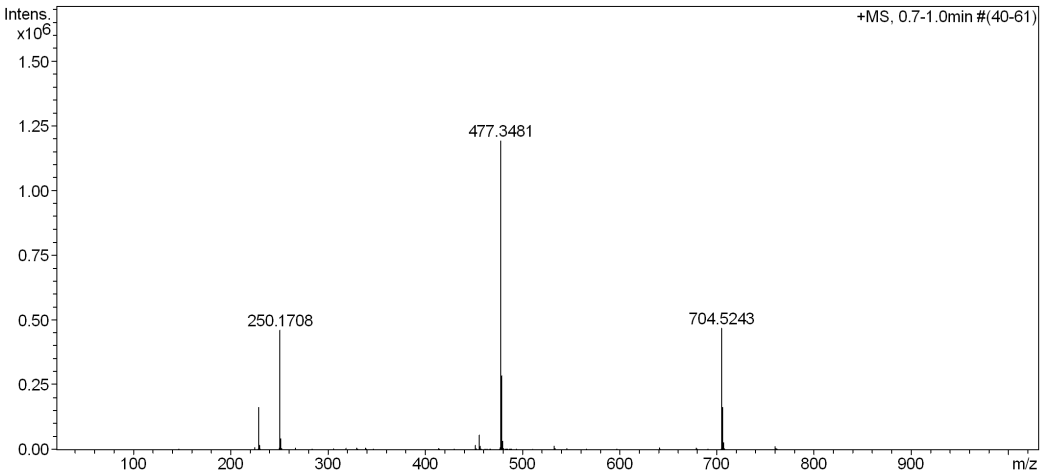
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



TIC +All MS





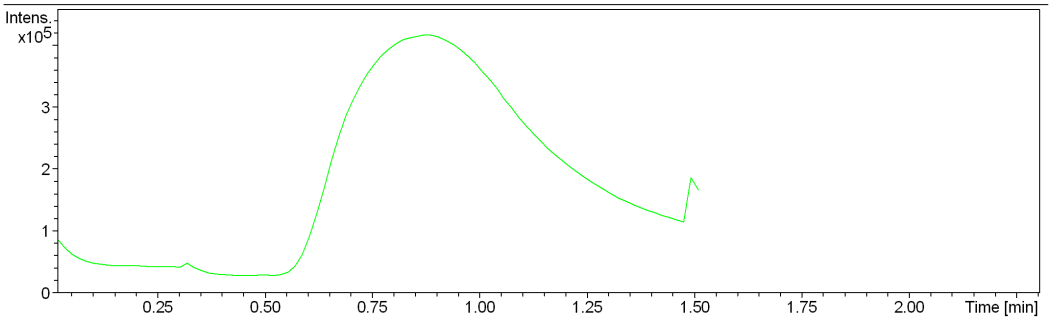
Display Report

Analysis Info

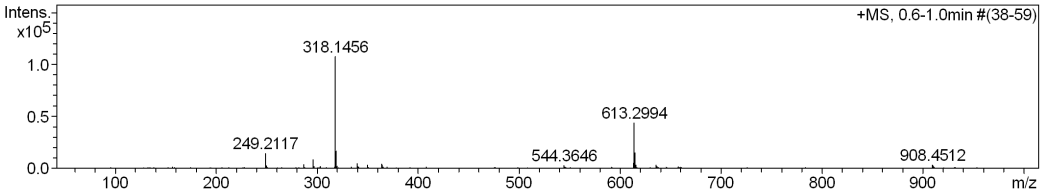
Analysis Name	D:\Data\Dogan\amer\RA-1-33.d	Acquisition Date	10/17/2018 12:06:33 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

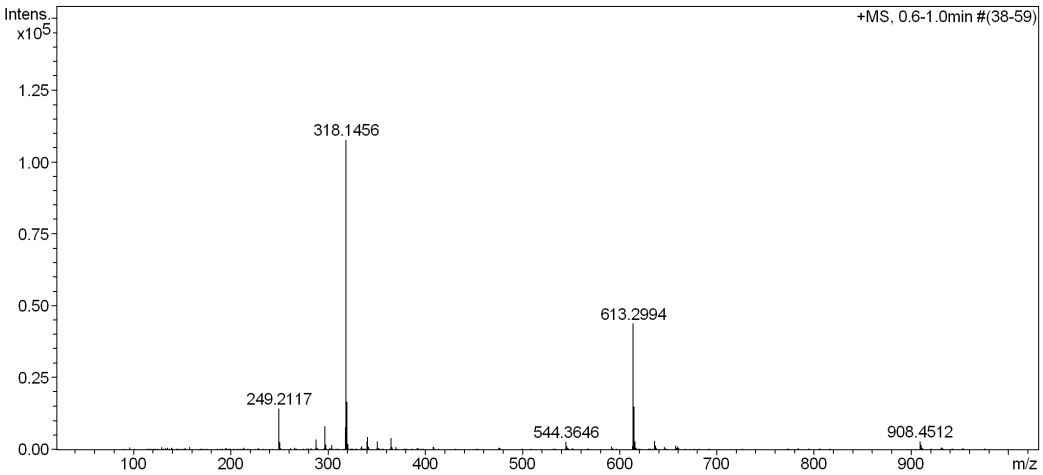
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



TIC +All MS

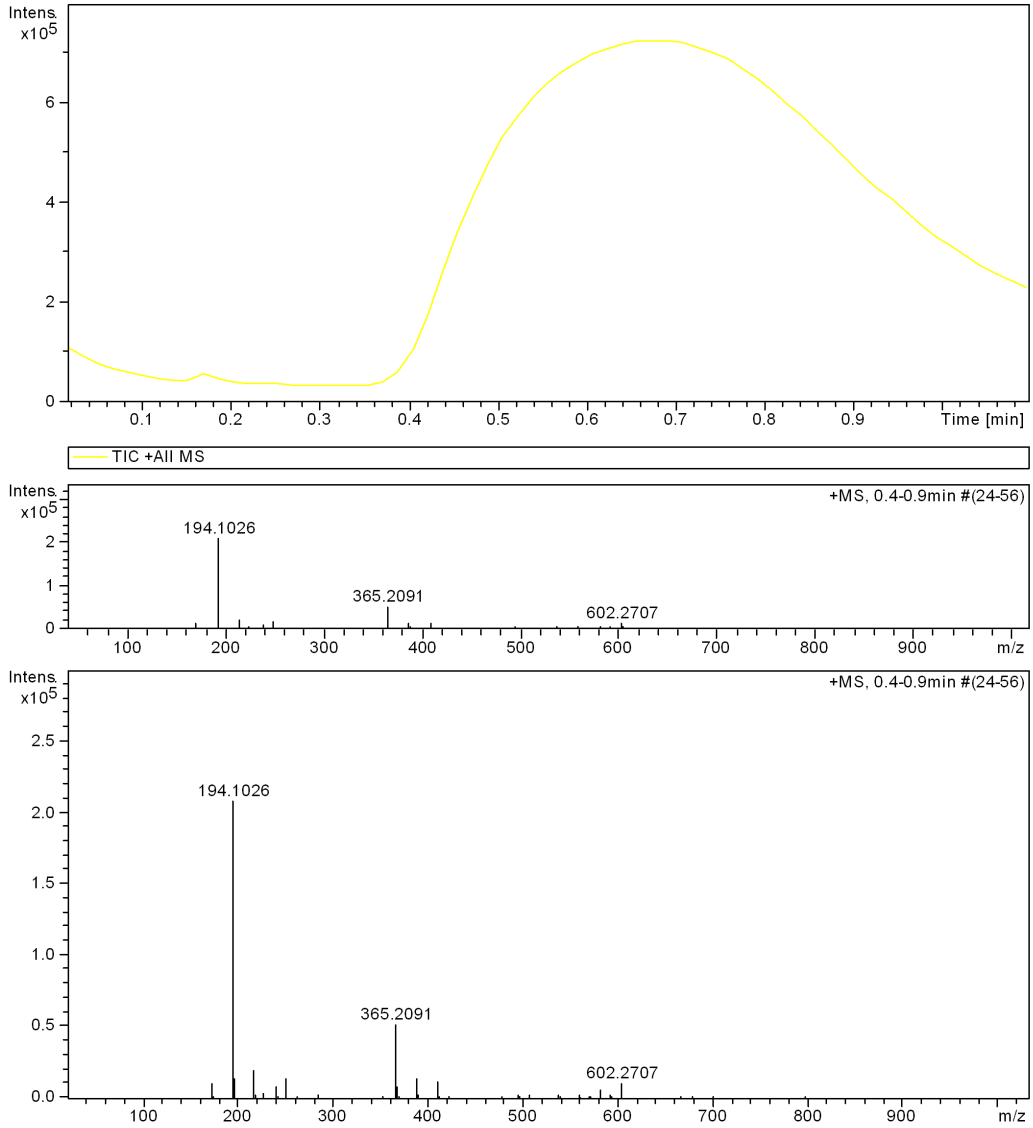




Generic Display Report

Analysis Info

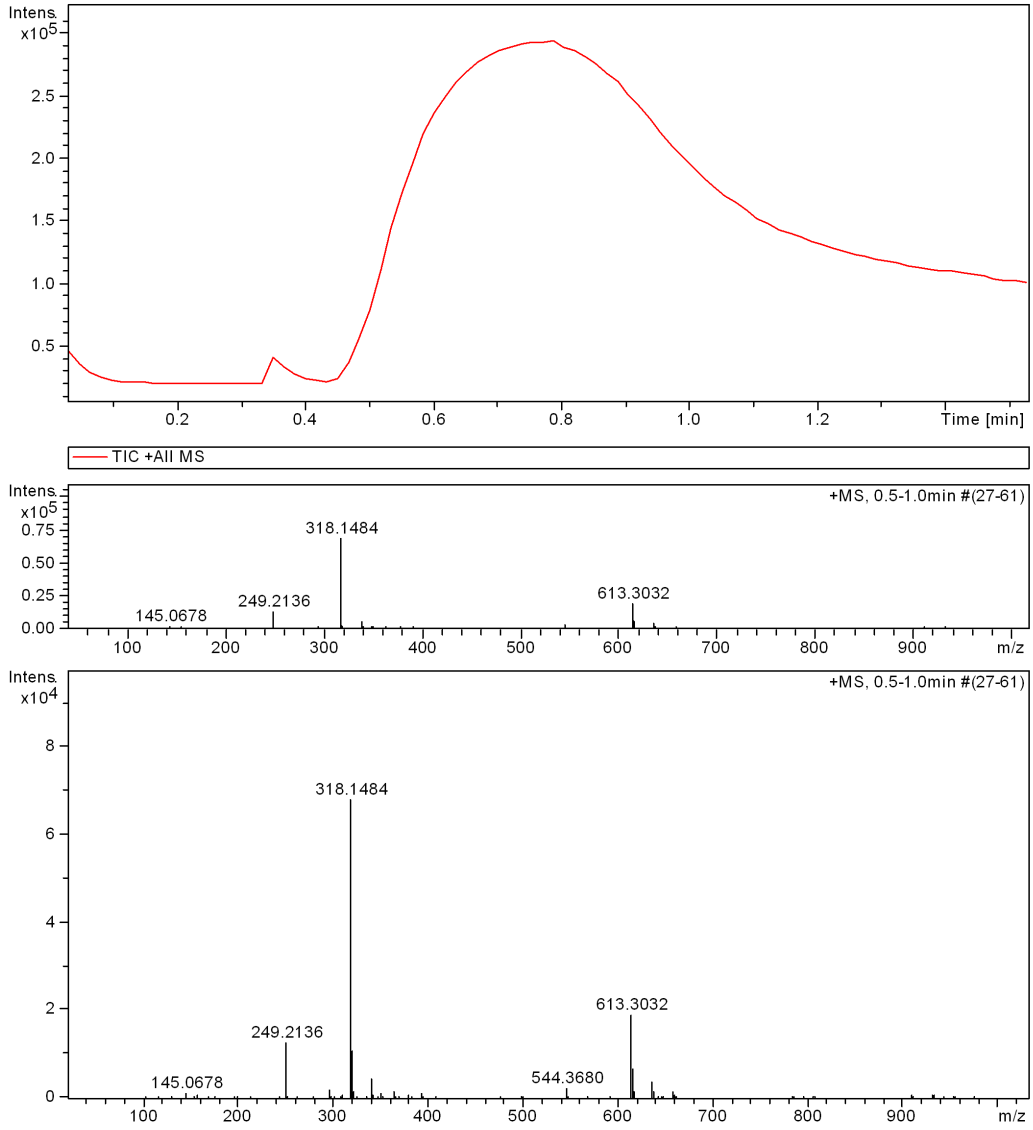
Analysis Name	D:\Data\Dogan\amer\RA-1-34.d	Acquisition Date	10/17/2018 12:11:57 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

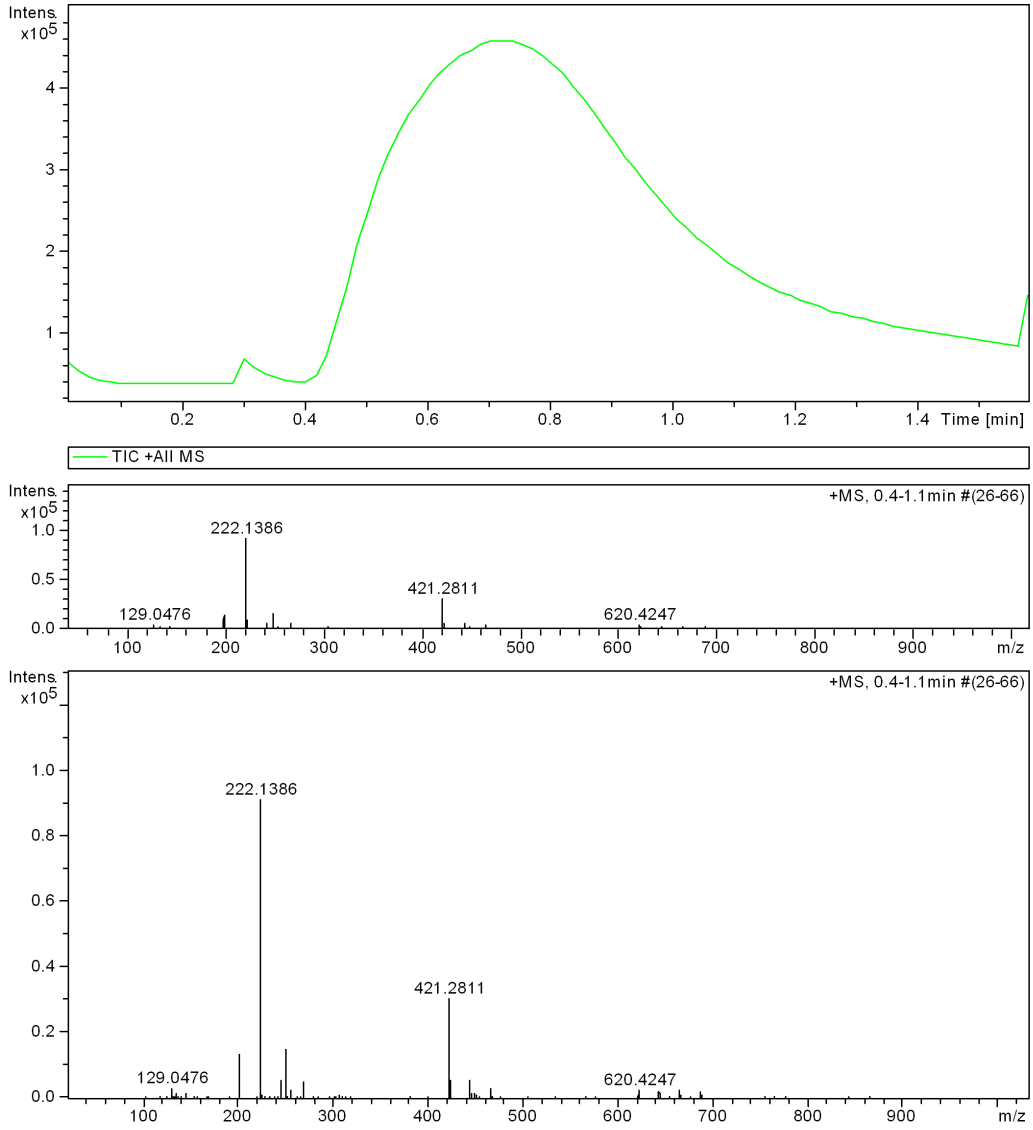
Analysis Name	D:\Data\Dogan\amer\RA-1-35.d	Acquisition Date	10/25/2018 1:09:03 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

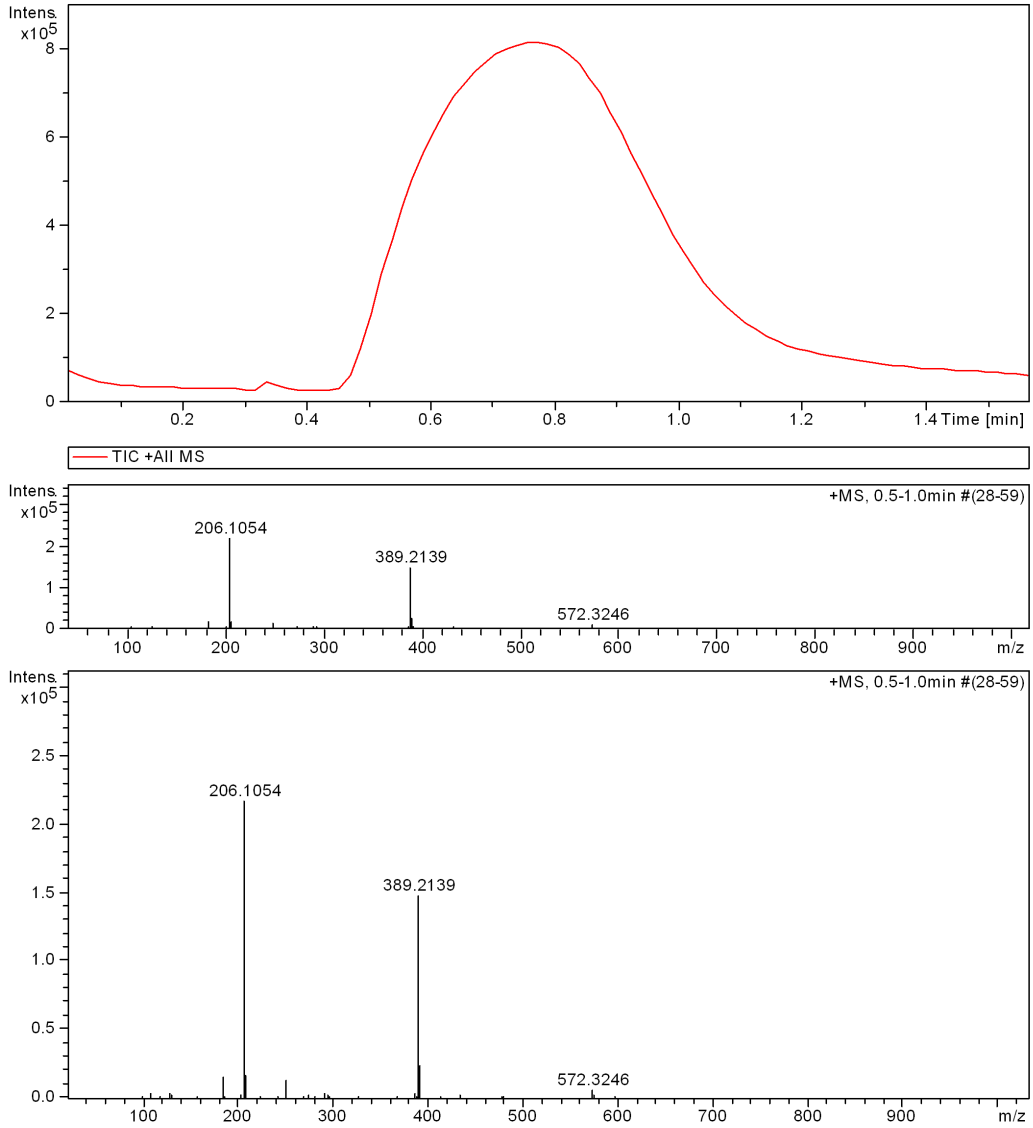
Analysis Name	D:\Data\Dogan\amer\RA-1-36.d	Acquisition Date	10/25/2018 1:15:10 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

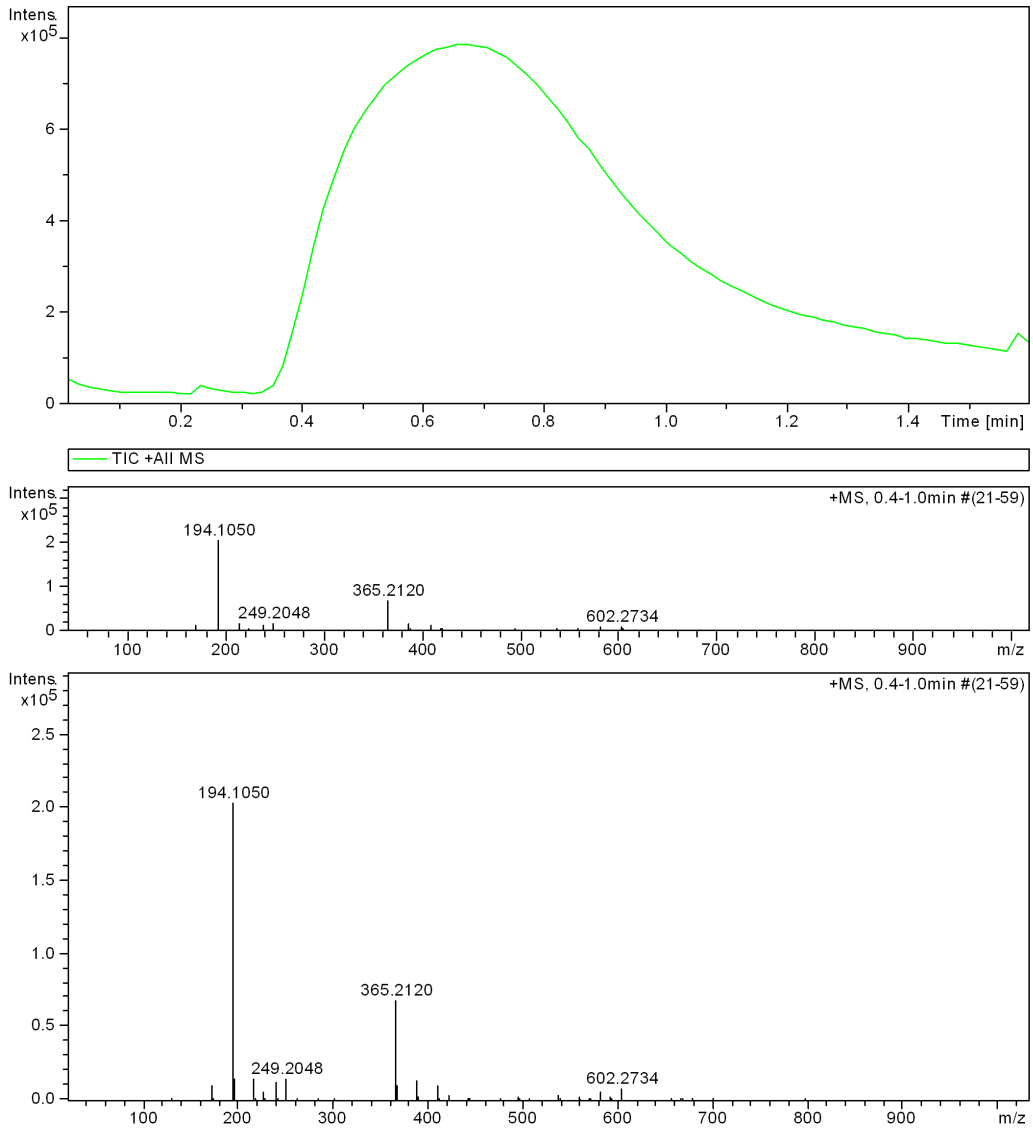
Analysis Name	D:\Data\Dogan\amer\RA-1-38.d	Acquisition Date	11/1/2018 2:41:53 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

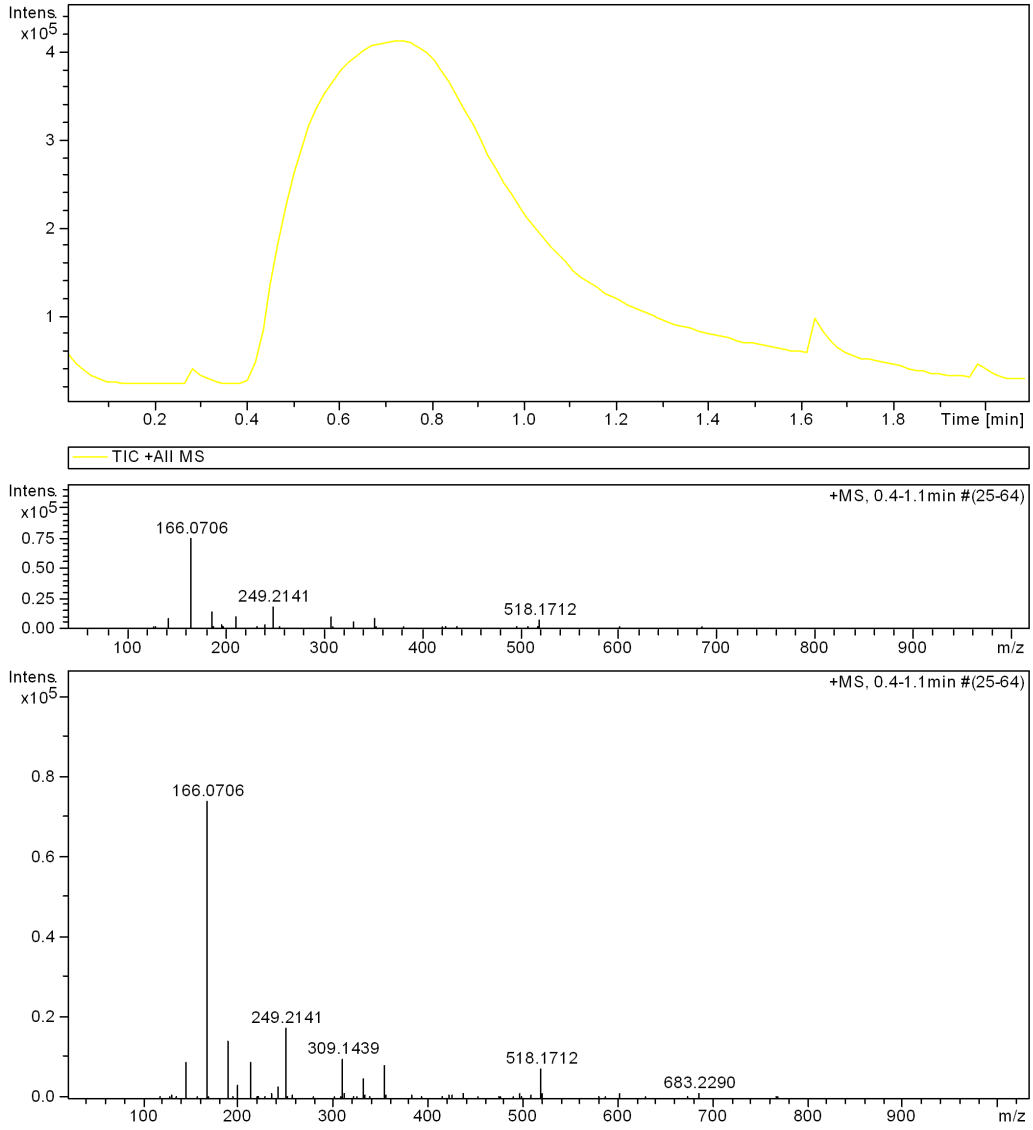
Analysis Name	D:\Data\Dogan\amer\RA-1-39.d	Acquisition Date	11/1/2018 2:47:48 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

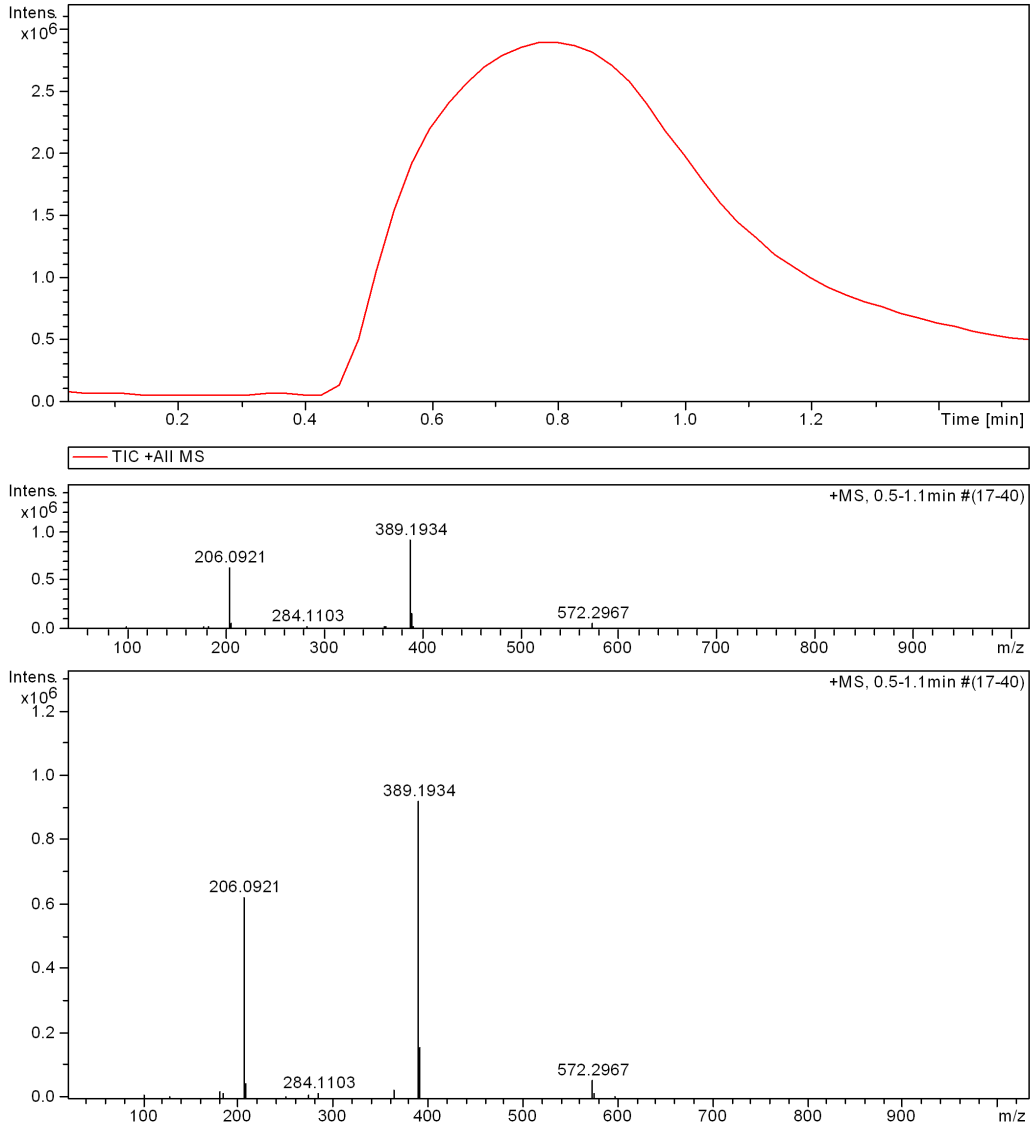
Analysis Name	D:\Data\Dogan\amer\RA-1-40.d	Acquisition Date	11/1/2018 2:52:48 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

Analysis Name	D:\Data\Dogan\amer\RA-1-41-1.d	Acquisition Date	11/7/2018 11:49:45 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



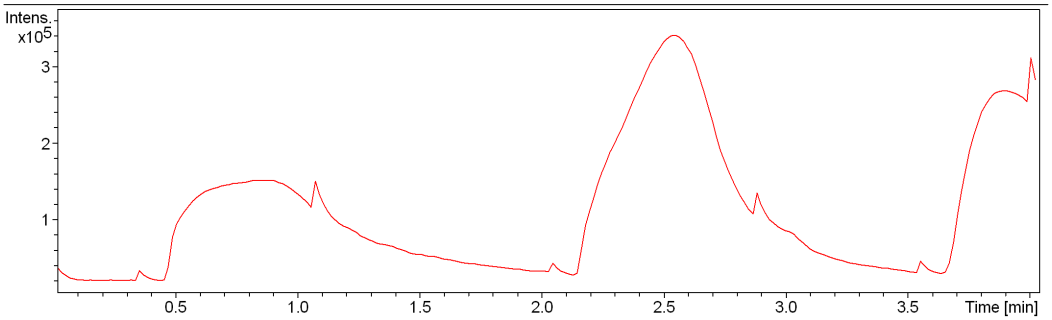
Display Report

Analysis Info

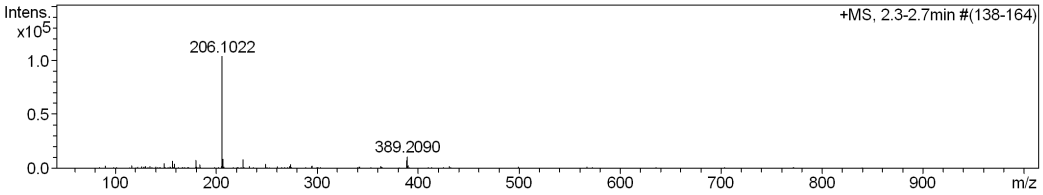
Analysis Name	D:\Data\Hadad\Leilani\RA-1-44.d	Acquisition Date	11/30/2018 3:07:10 PM
Method	Tune_Low.m	Operator	lottidiaz.1
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

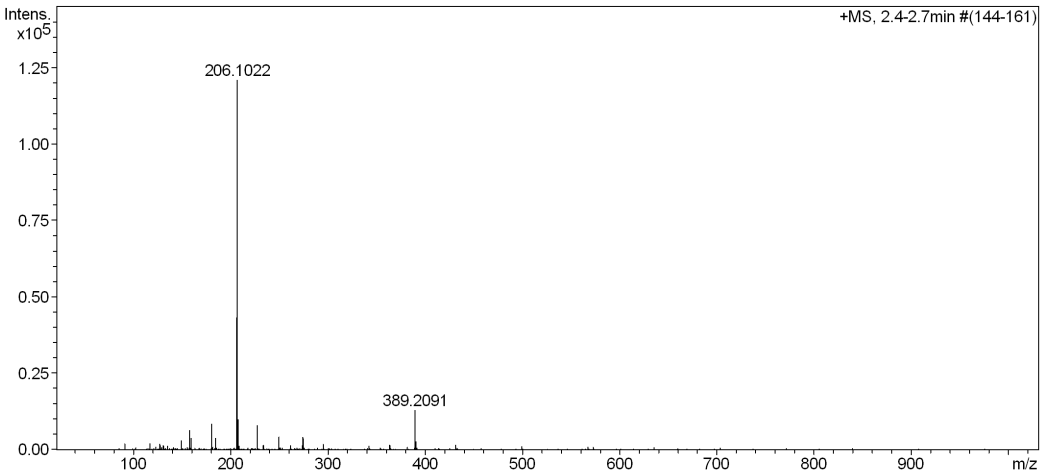
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



TIC +All MS

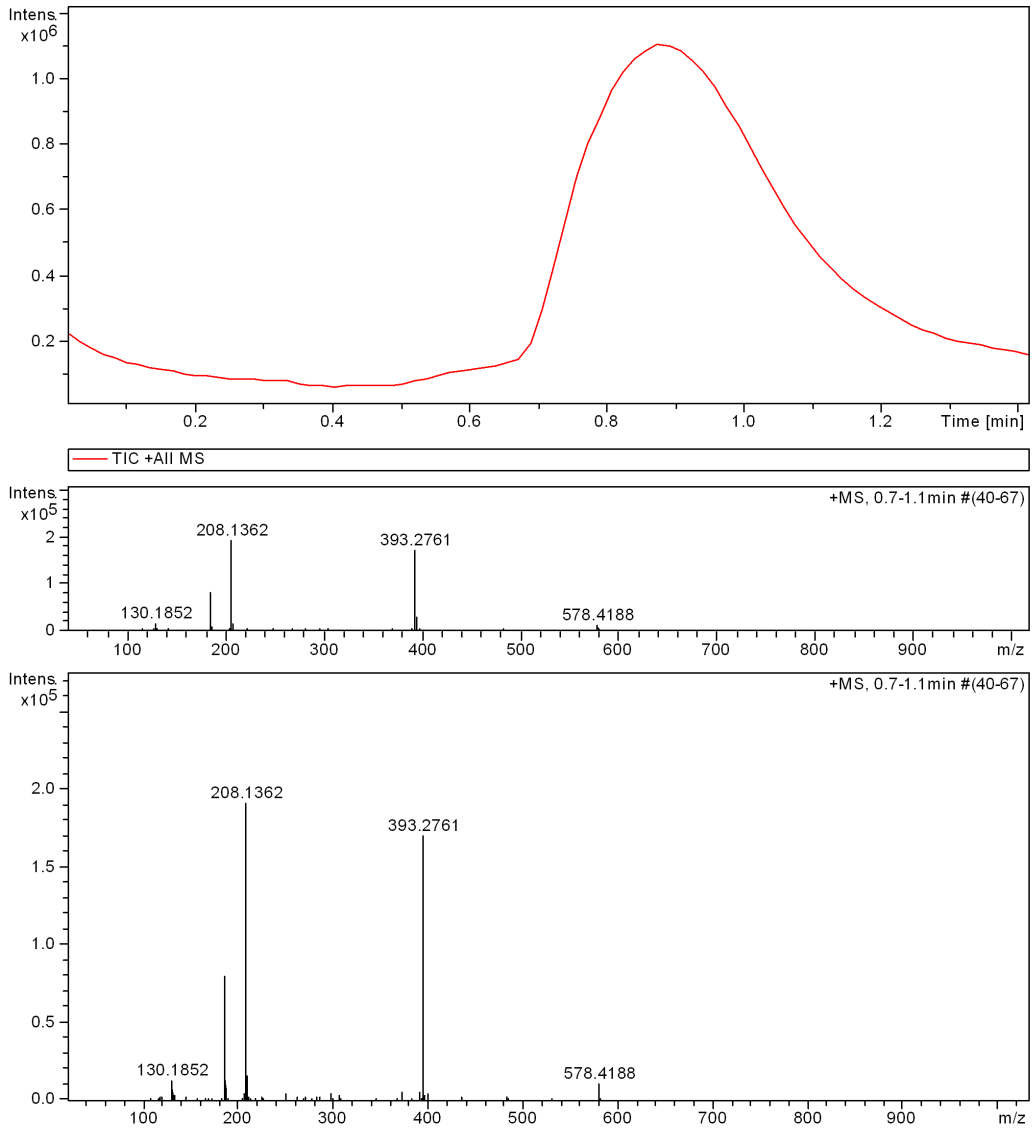




Generic Display Report

Analysis Info

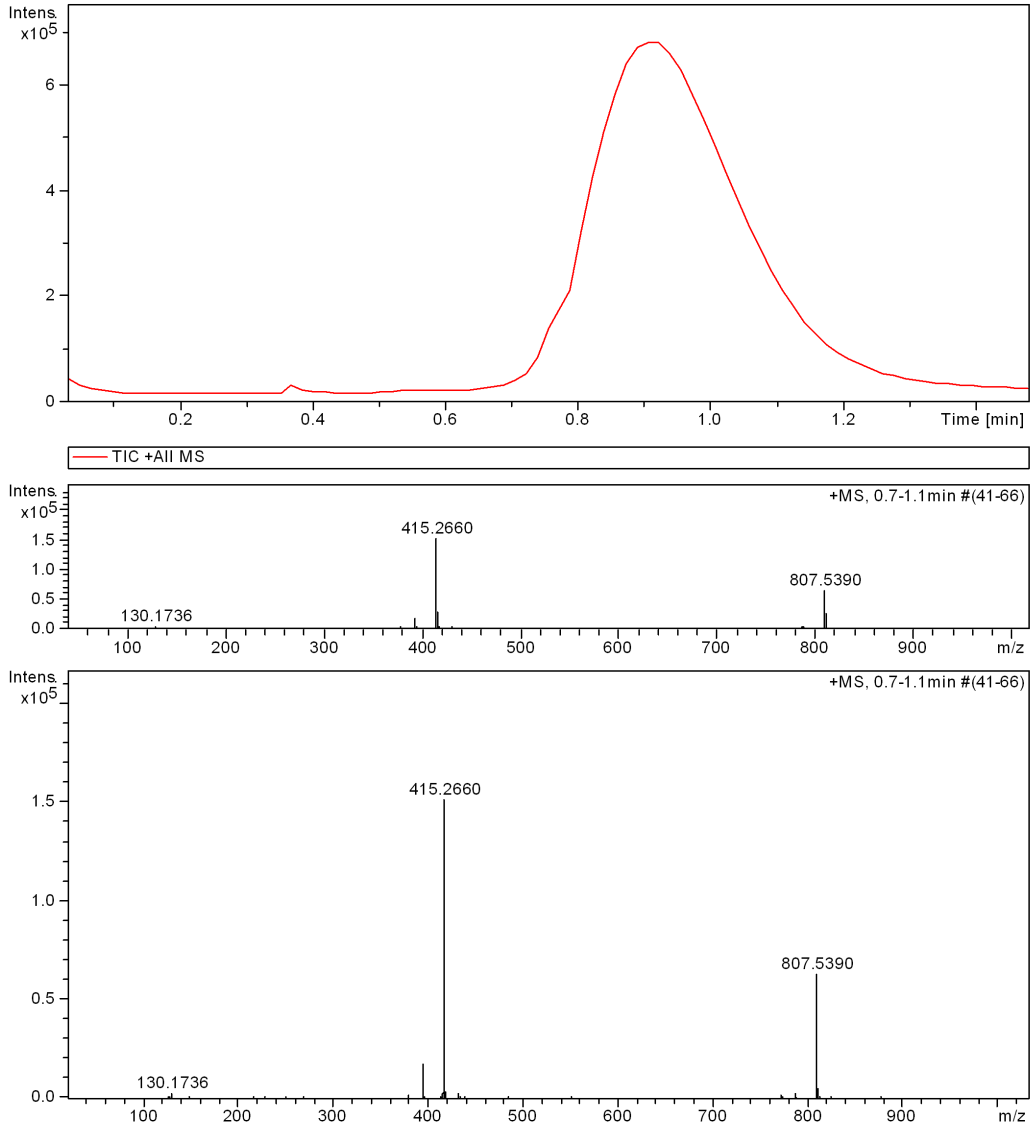
Analysis Name	D:\Data\Dogan\amer\RA-1-45.d	Acquisition Date	11/28/2018 9:09:46 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

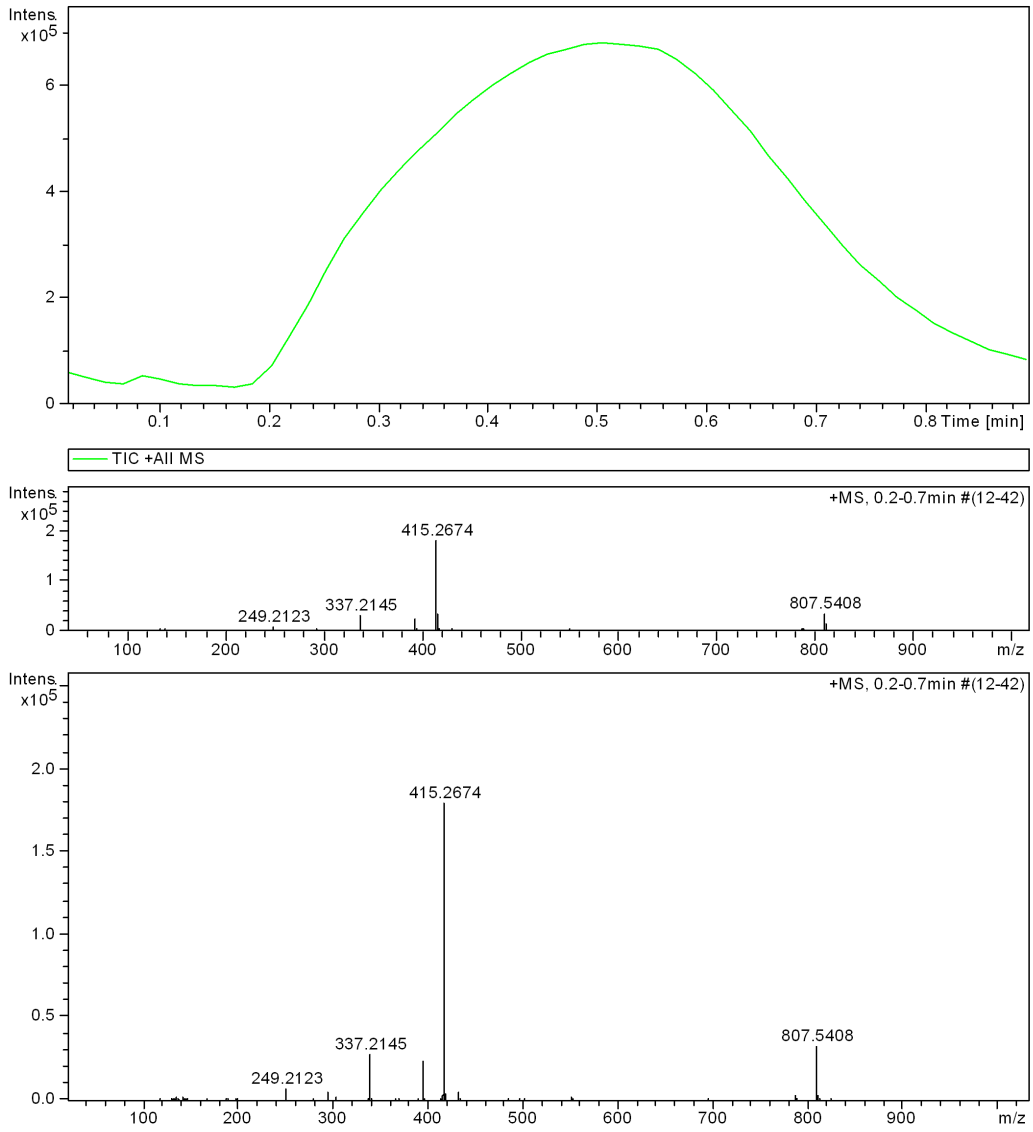
Analysis Name	D:\Data\Dogan\amer\RA-1-47-2.d	Acquisition Date	1/15/2019 12:43:45 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

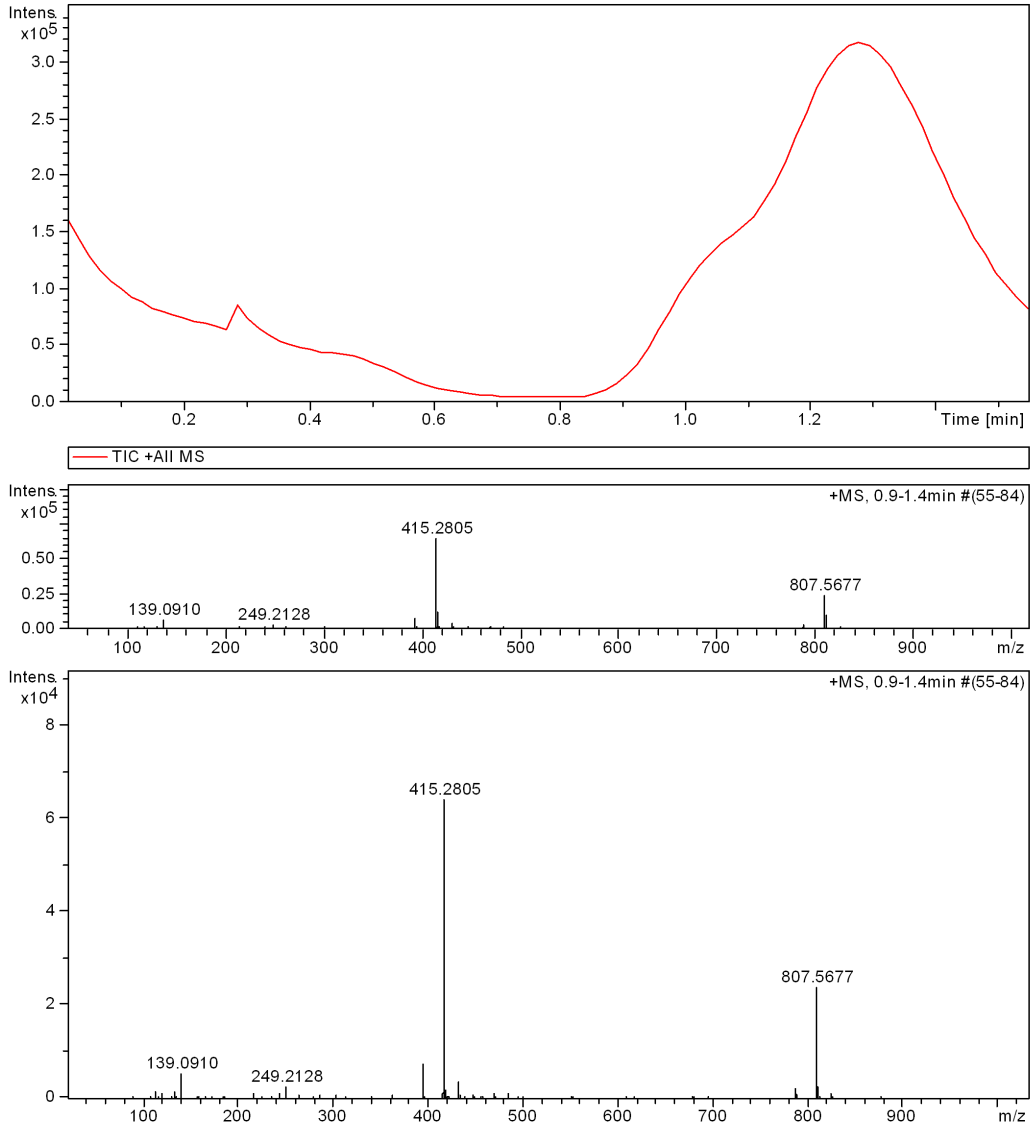
Analysis Name	D:\Data\Dogan\amer\RA-1-48.d	Acquisition Date	1/15/2019 12:53:34 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

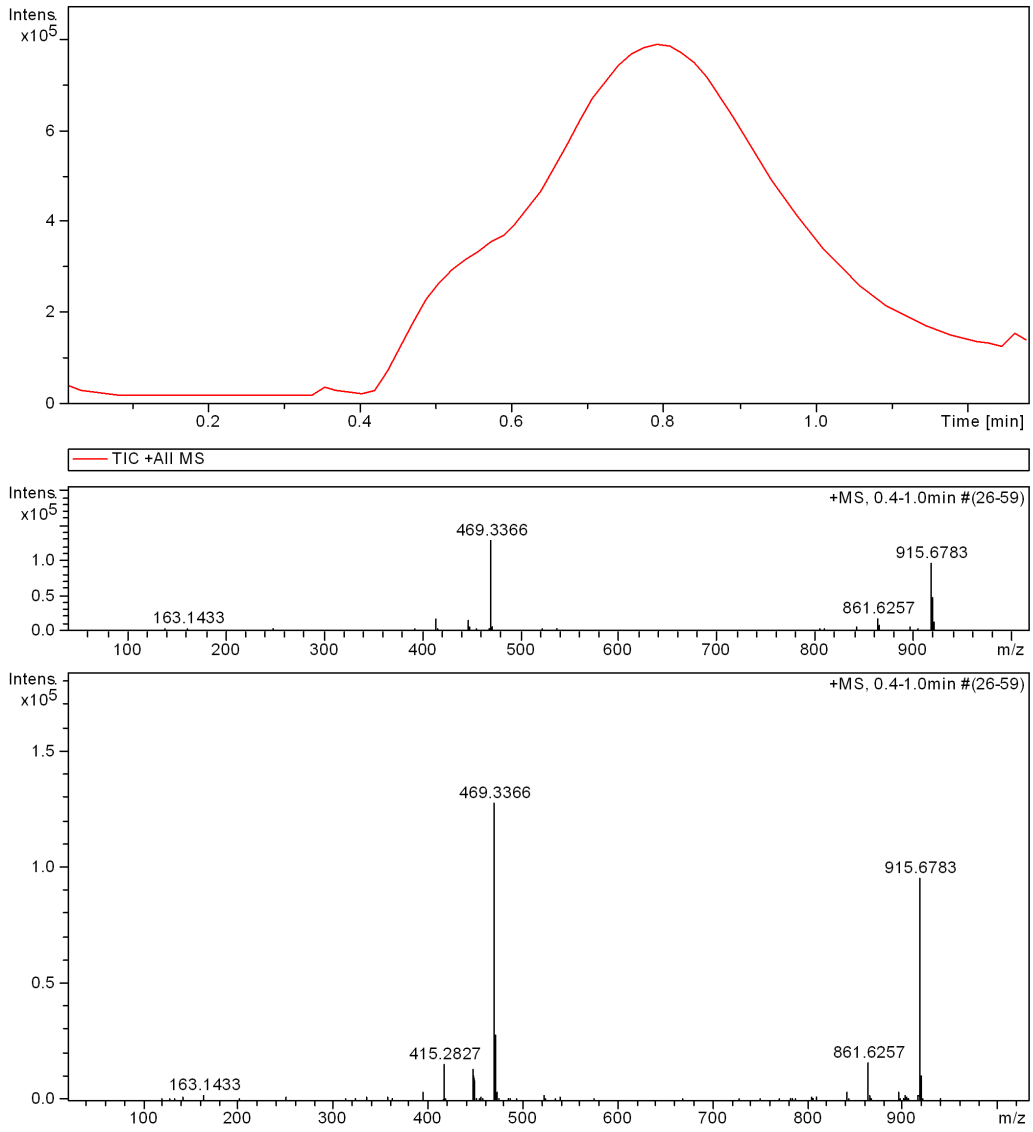
Analysis Name	D:\Data\Dogan\amer\RA-1-49.d	Acquisition Date	1/17/2019 9:27:20 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

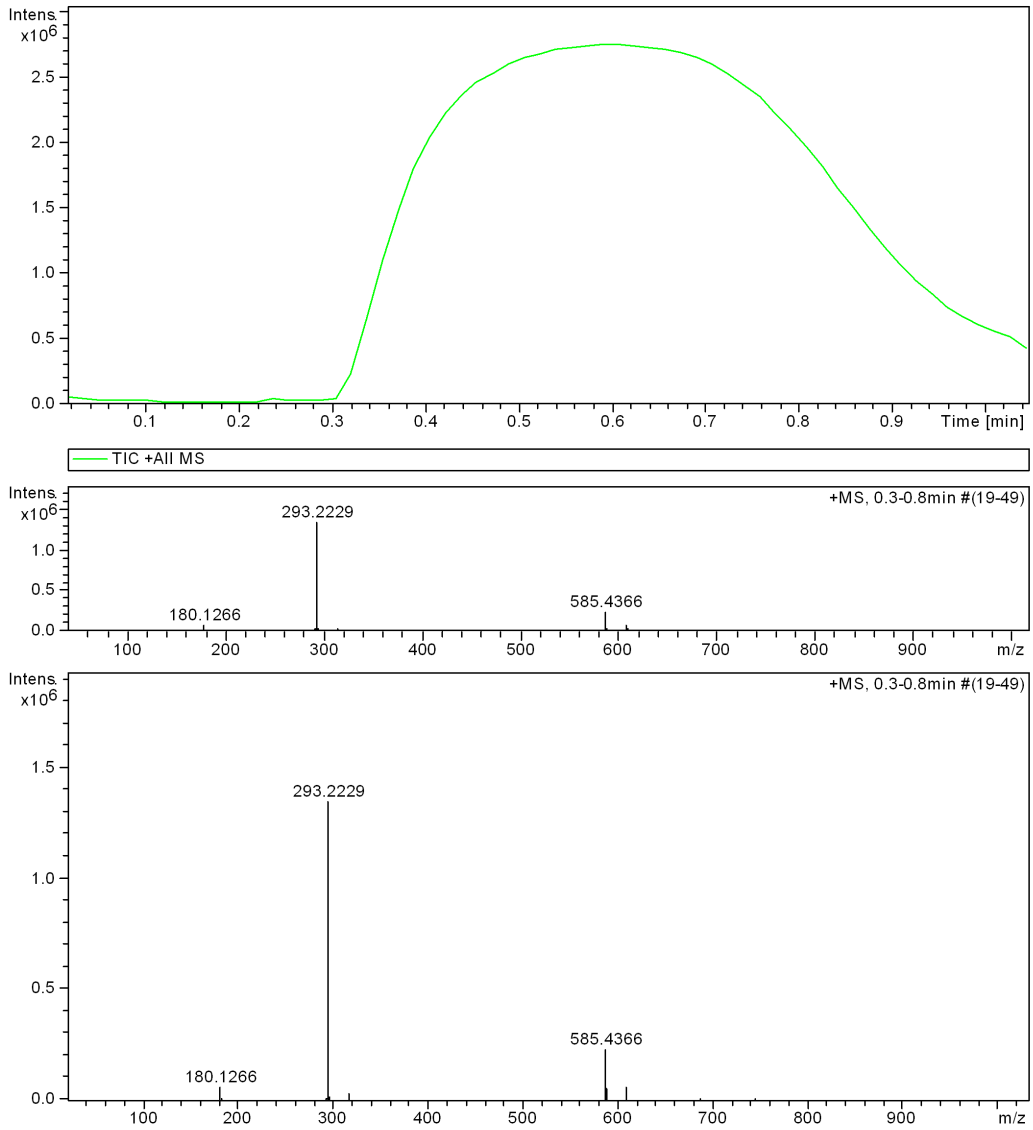
Analysis Name	D:\Data\Dogan\amer\RA-1-50.d	Acquisition Date	1/23/2019 4:47:58 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

Analysis Name	D:\Data\Dogan\amer\RA-1-51.d	Acquisition Date	1/24/2019 9:31:30 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



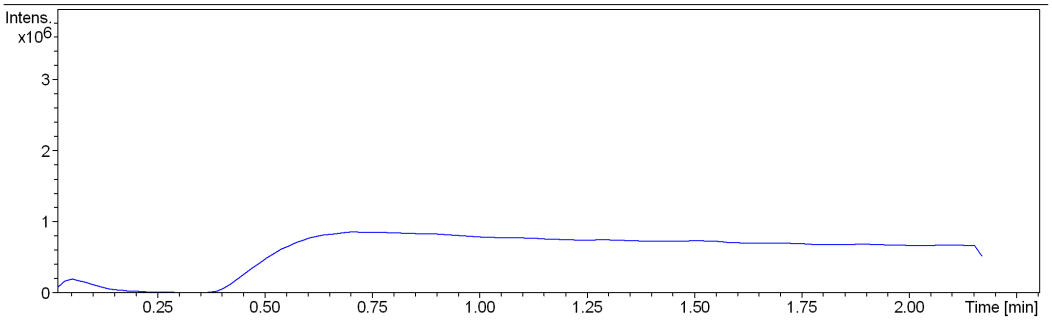
Display Report

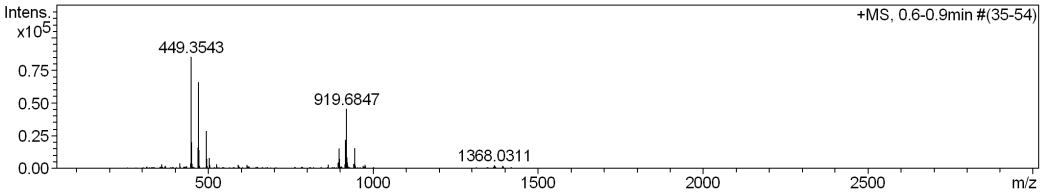
Analysis Info

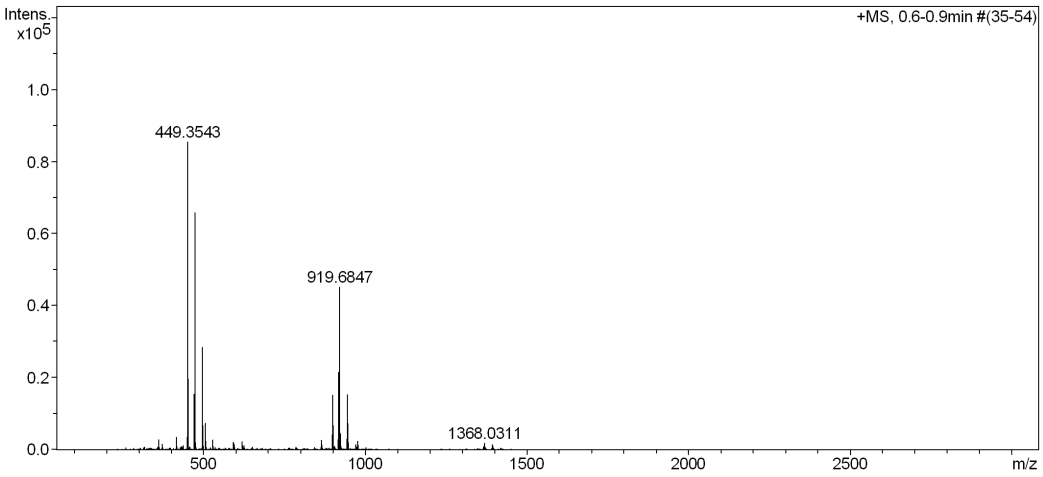
Analysis Name	D:\Data\Hadad\Border\RA-I-52.d	Acquisition Date	2/2/2019 2:21:02 PM
Method	Tune_Wide.m	Operator	border.26
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Source



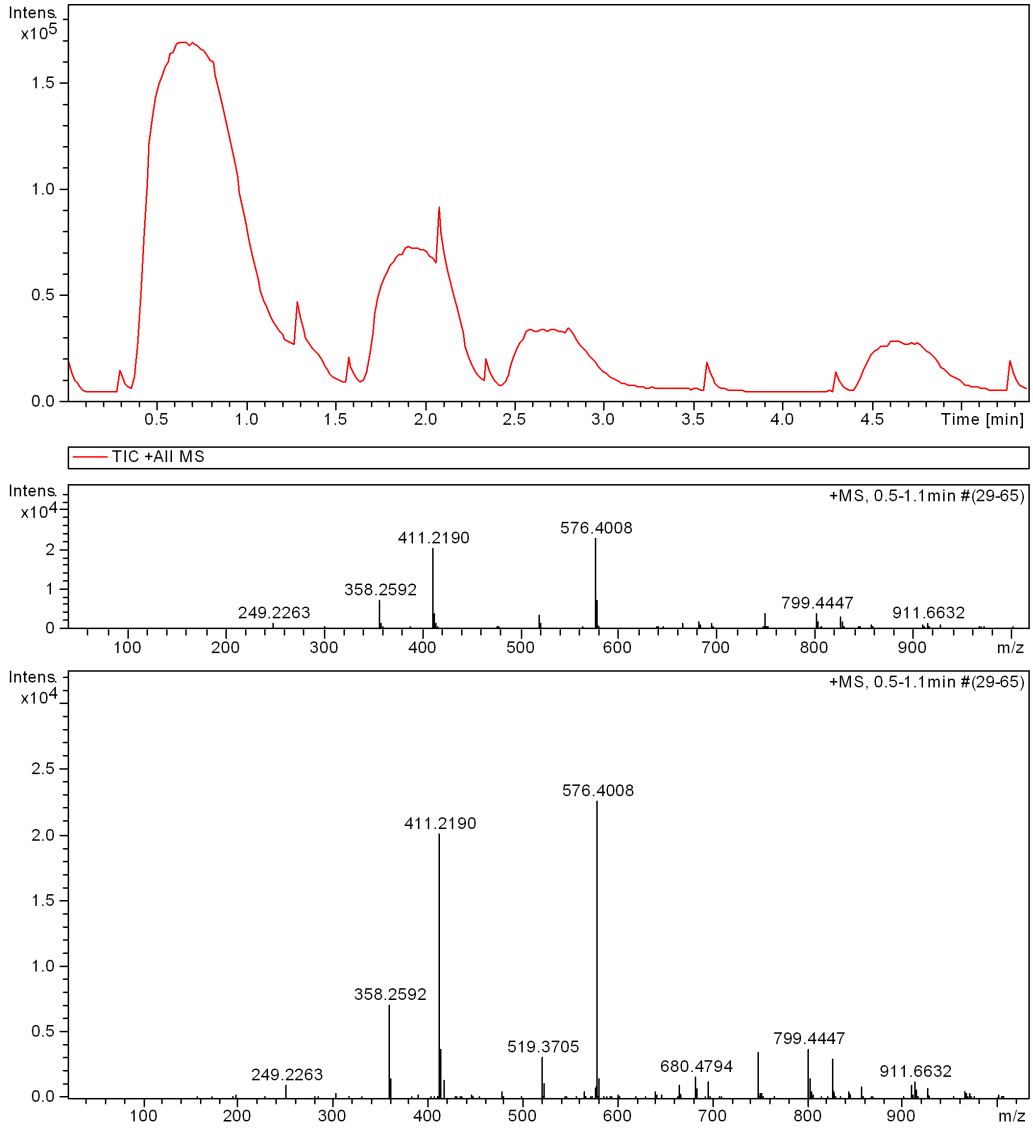




Generic Display Report

Analysis Info

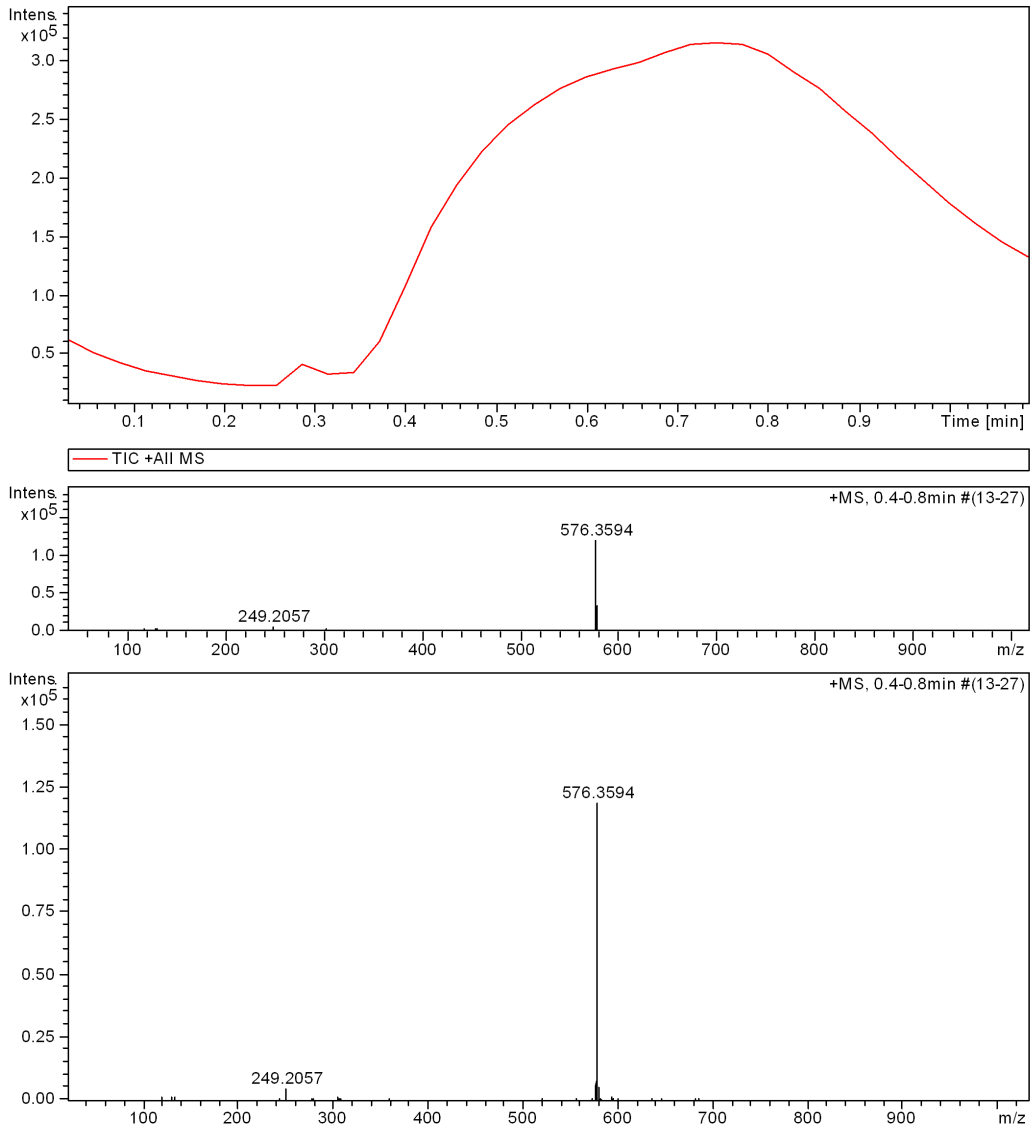
Analysis Name	D:\Data\Dogan\amer\RA-1-53.d	Acquisition Date	2/12/2019 3:49:02 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

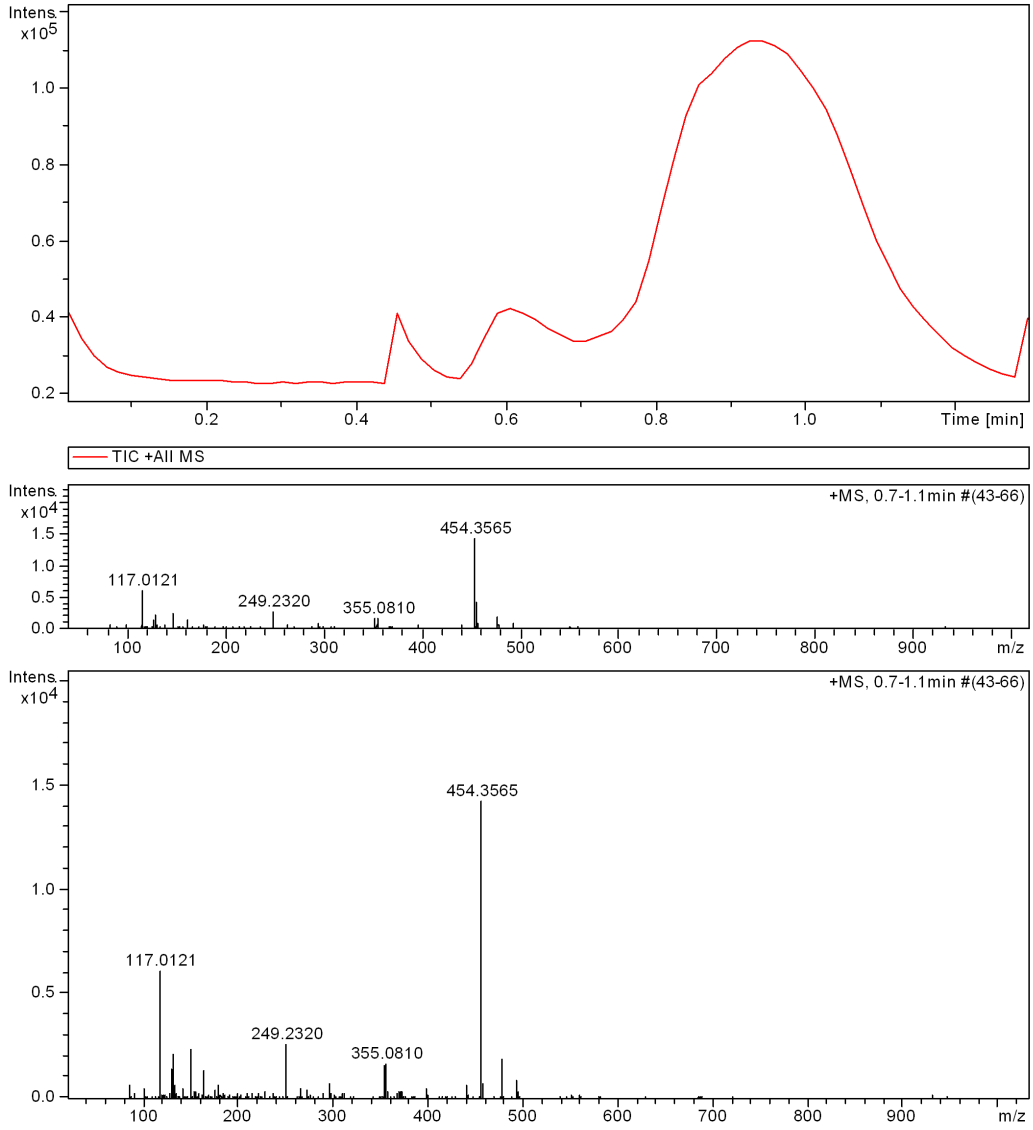
Analysis Name	D:\Data\Dogan\amer\RA-1-56.d	Acquisition Date	3/6/2019 9:29:00 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

Analysis Name	D:\Data\Dogan\amer\RA-1-57.d	Acquisition Date	3/20/2019 10:54:40 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



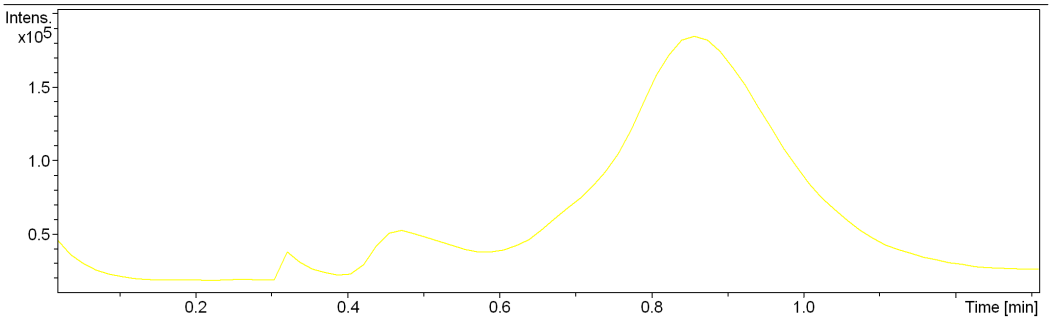
Display Report

Analysis Info

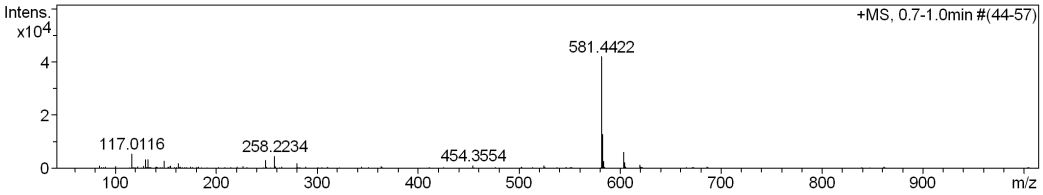
Analysis Name	D:\Data\Dogan\amer\RA-1-58-2.d	Acquisition Date	3/28/2019 8:56:36 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

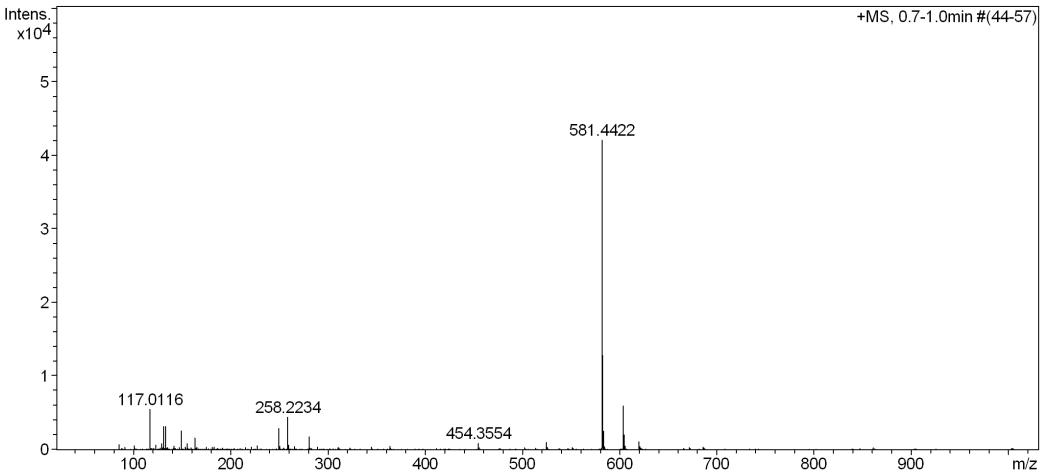
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



TIC +All MS





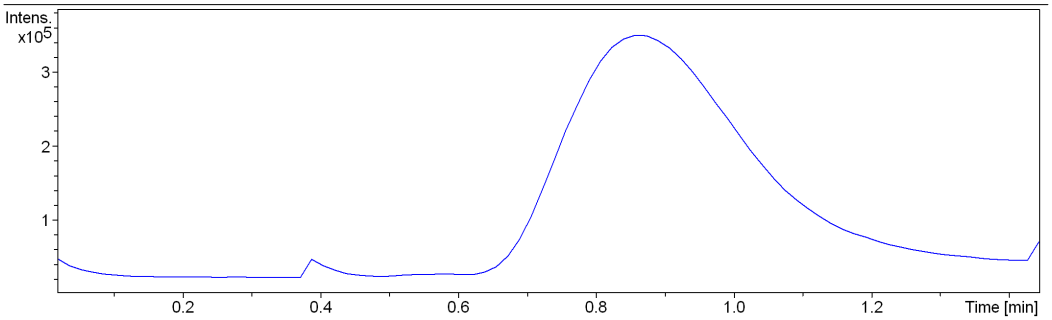
Display Report

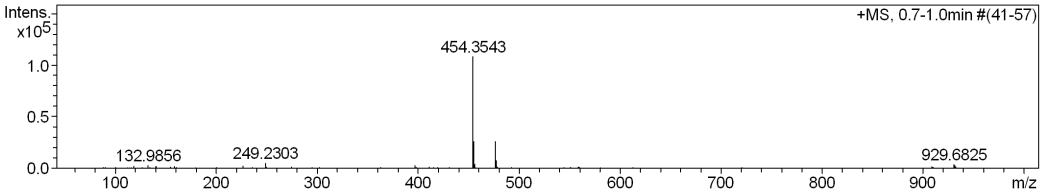
Analysis Info

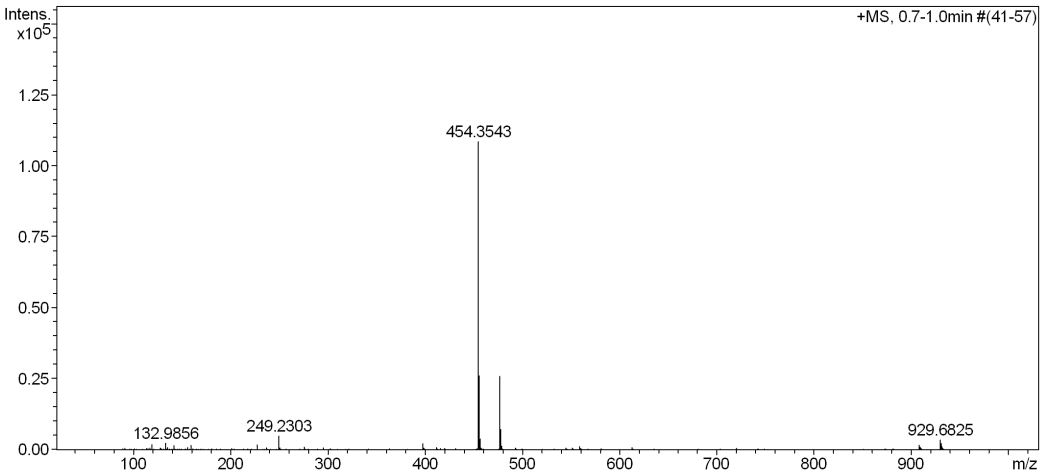
Analysis Name	D:\Data\Dogan\amer\RA-1-59.d	Acquisition Date	3/28/2019 8:45:46 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste







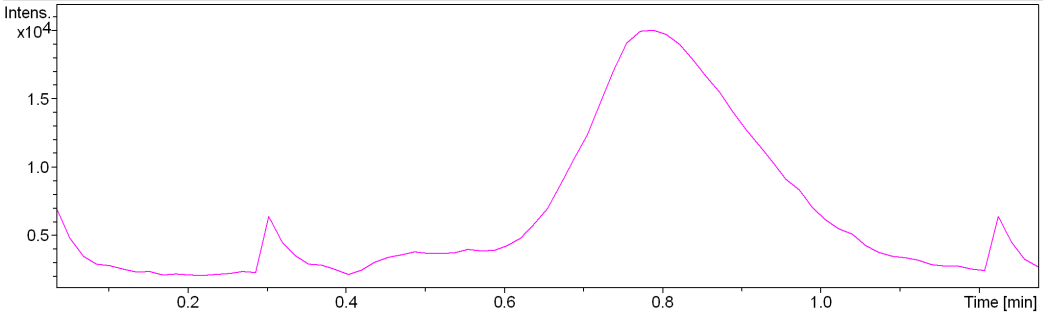
Display Report

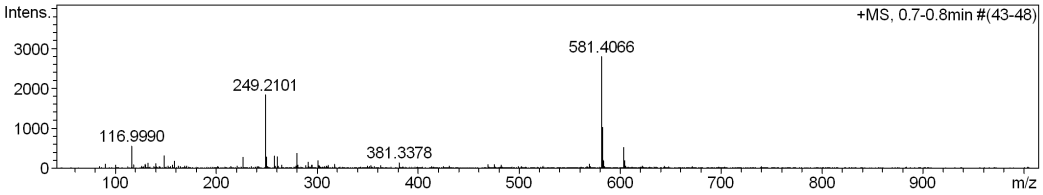
Analysis Info

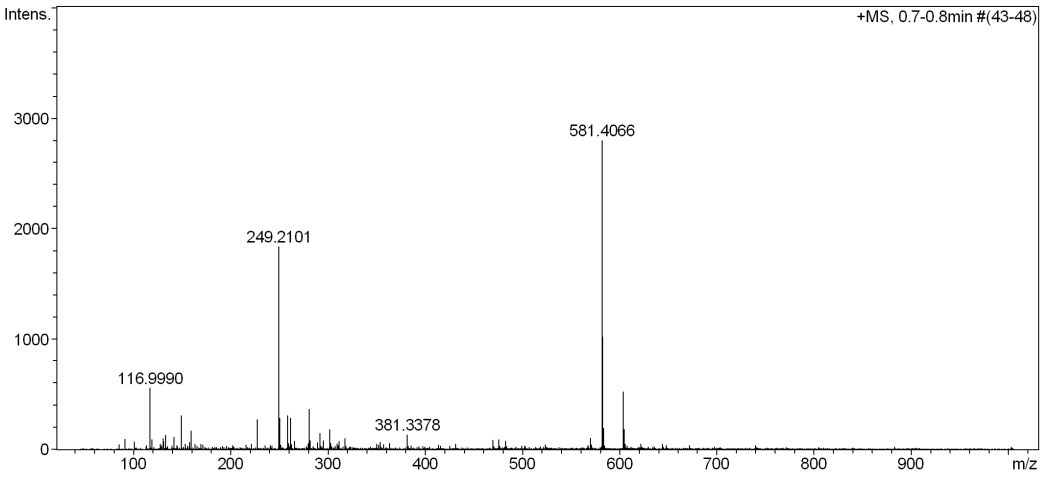
Analysis Name	D:\Data\Dogan\amer\RA-1-60.d	Acquisition Date	4/8/2019 9:18:01 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



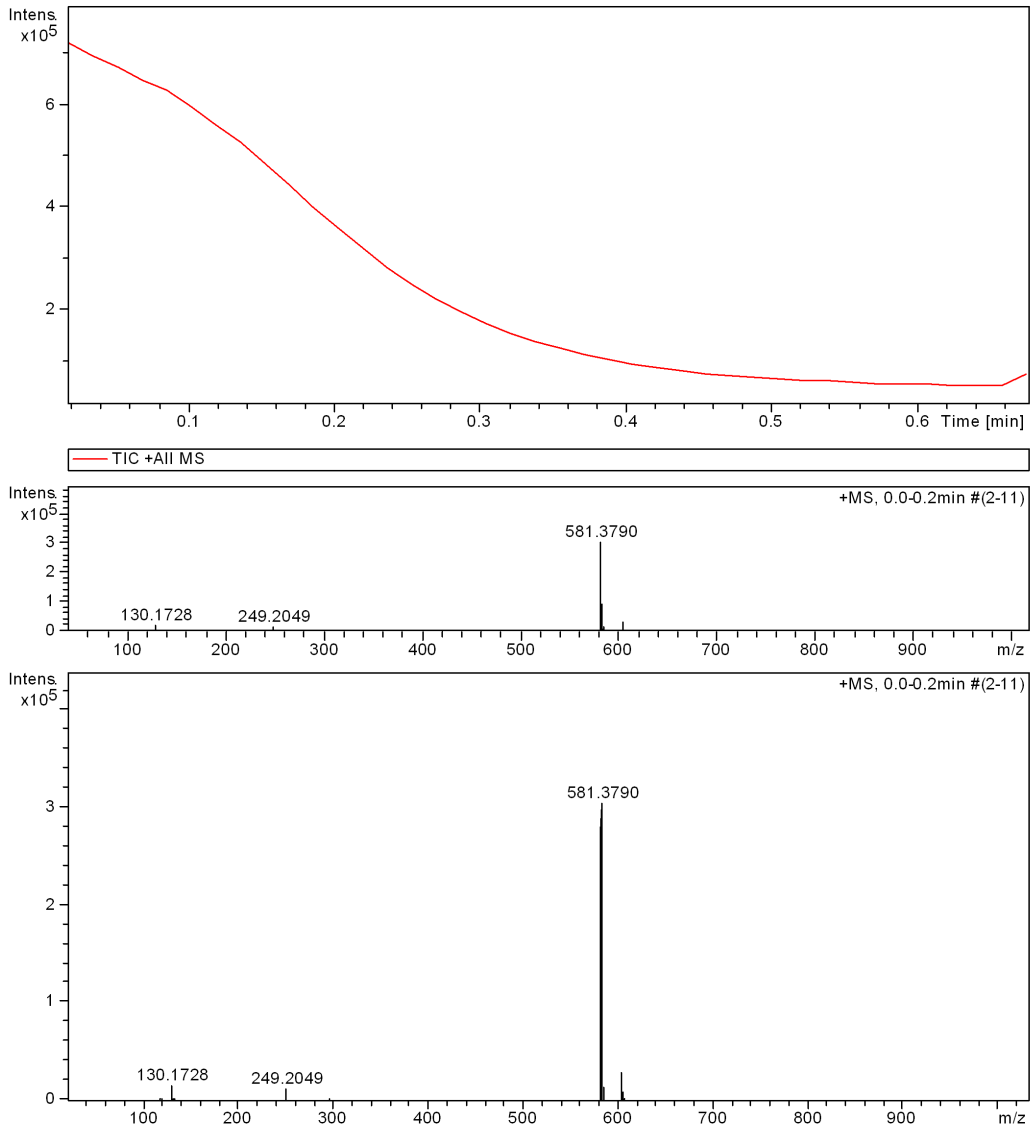




Generic Display Report

Analysis Info

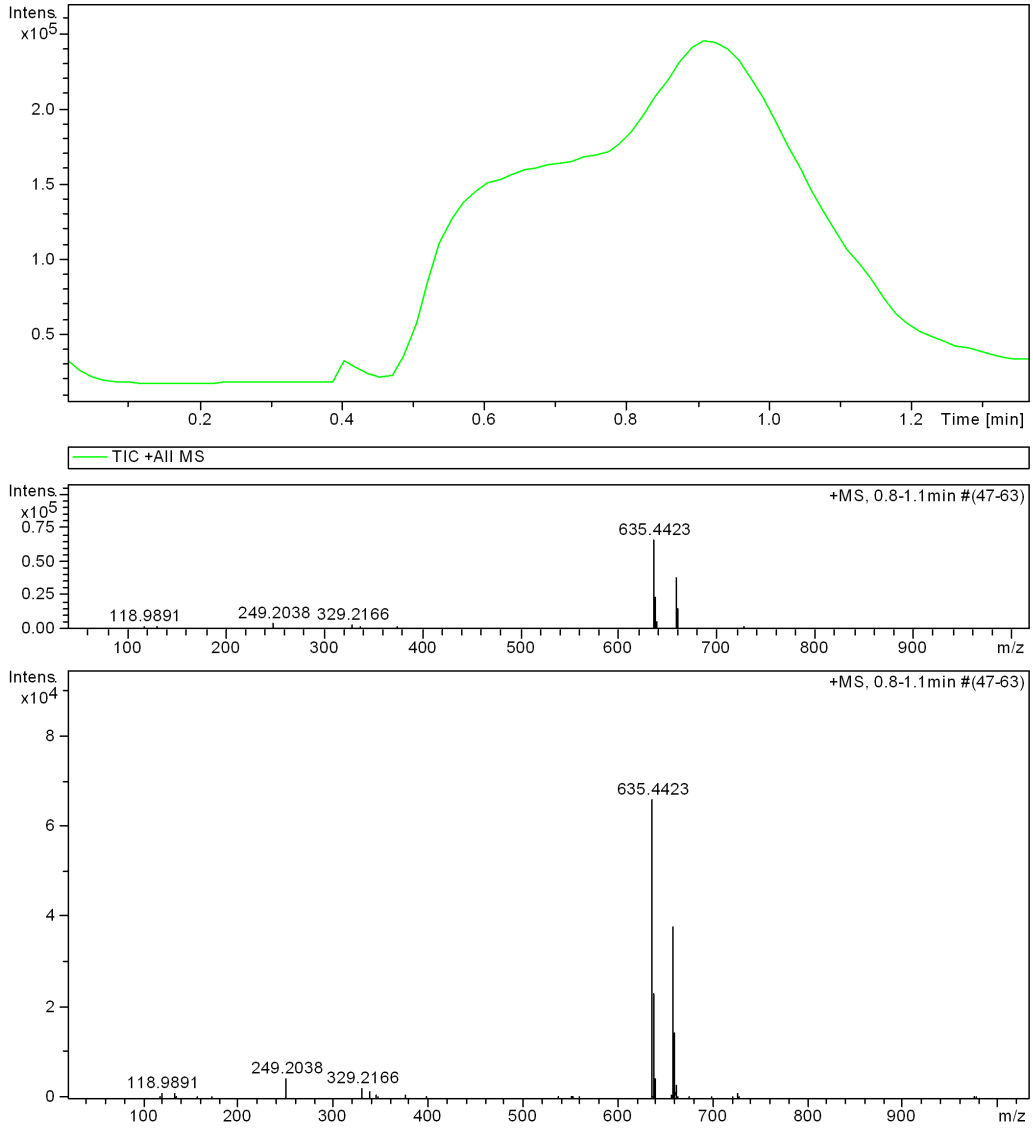
Analysis Name	D:\Data\Dogan\amer\RA-1-61-3.d	Acquisition Date	4/15/2019 12:54:25 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

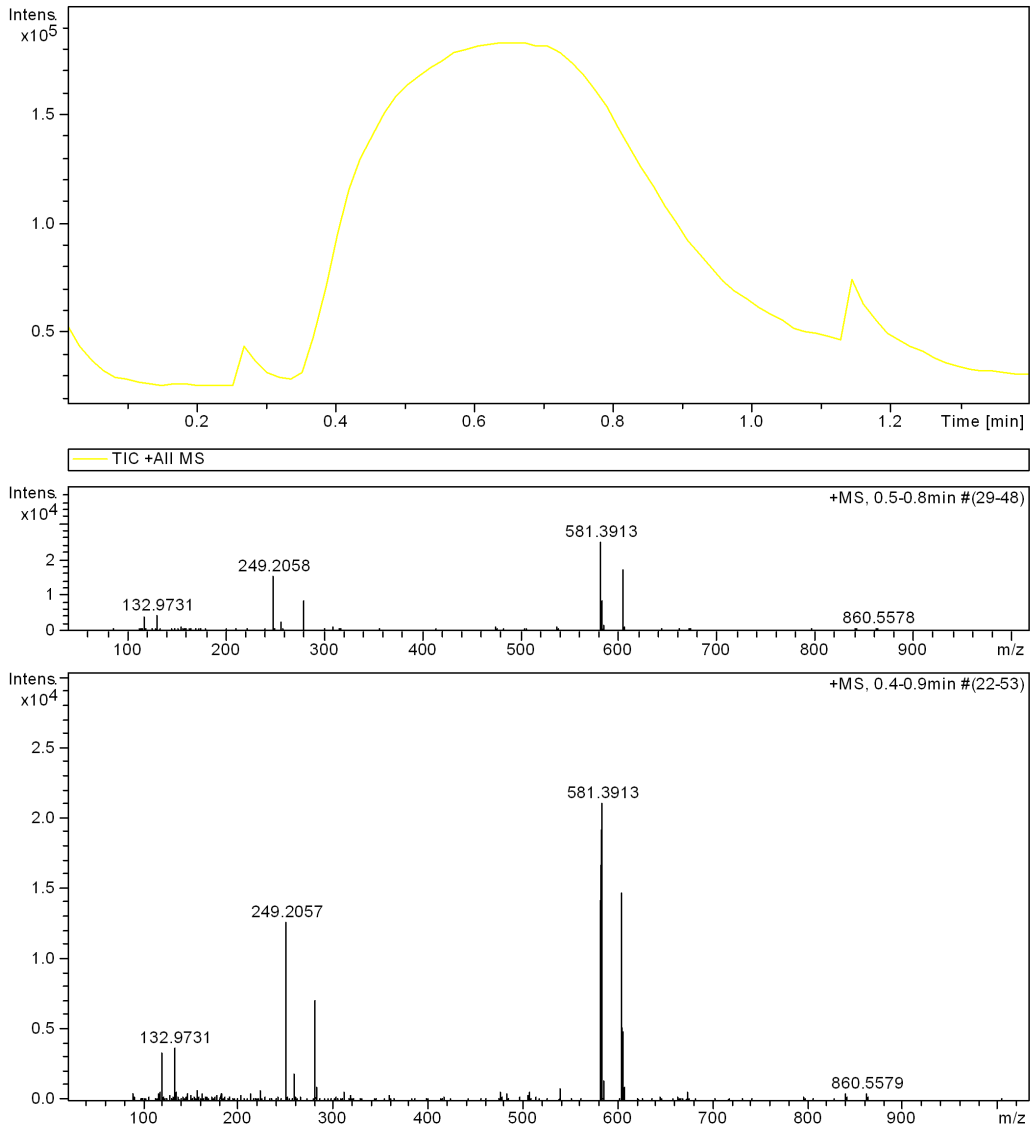
Analysis Name	D:\Data\Dogan\amer\RA-1-62-2.d	Acquisition Date	4/18/2019 9:21:13 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

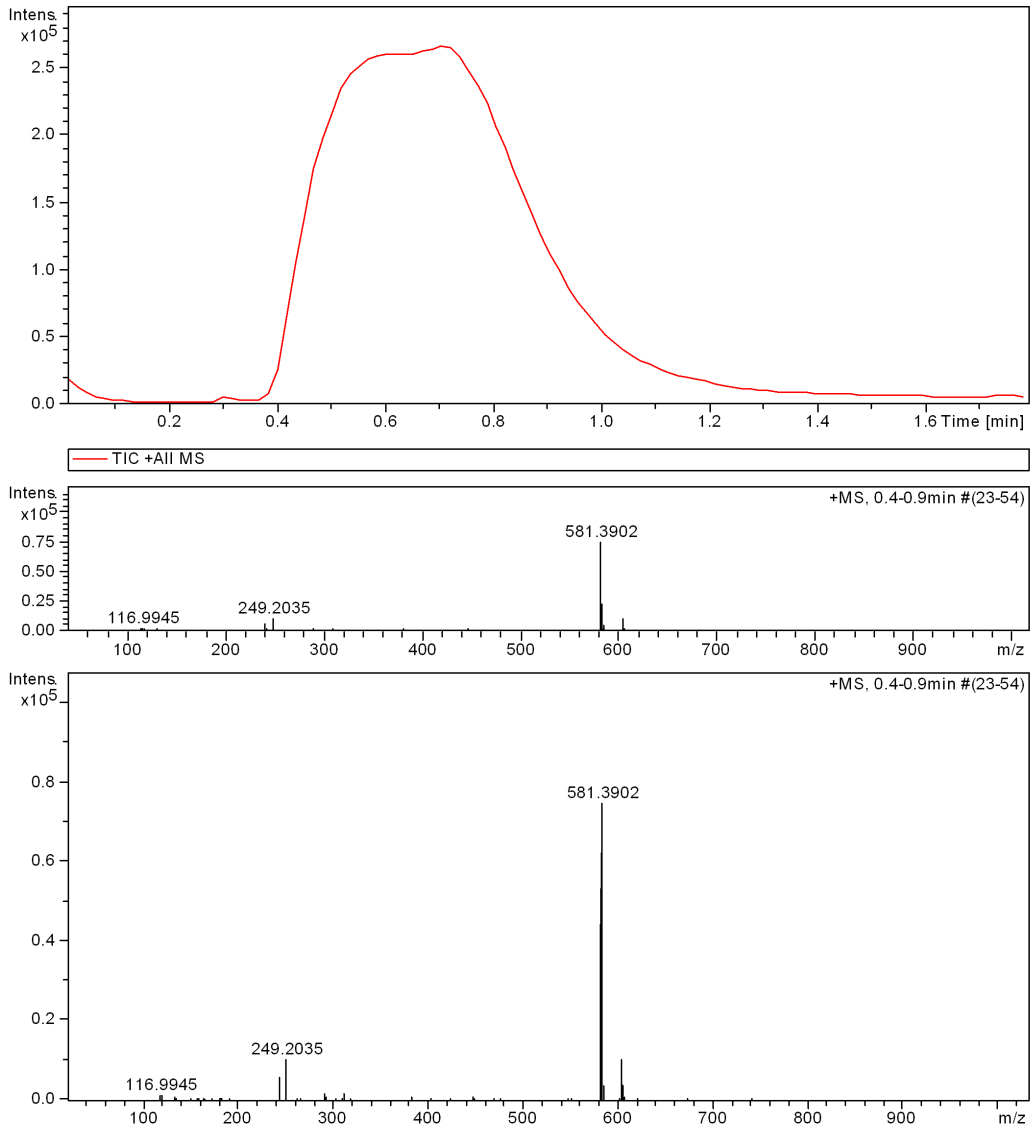
Analysis Name	D:\Data\Dogan\amer\RA-1-63.d	Acquisition Date	4/15/2019 1:03:29 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

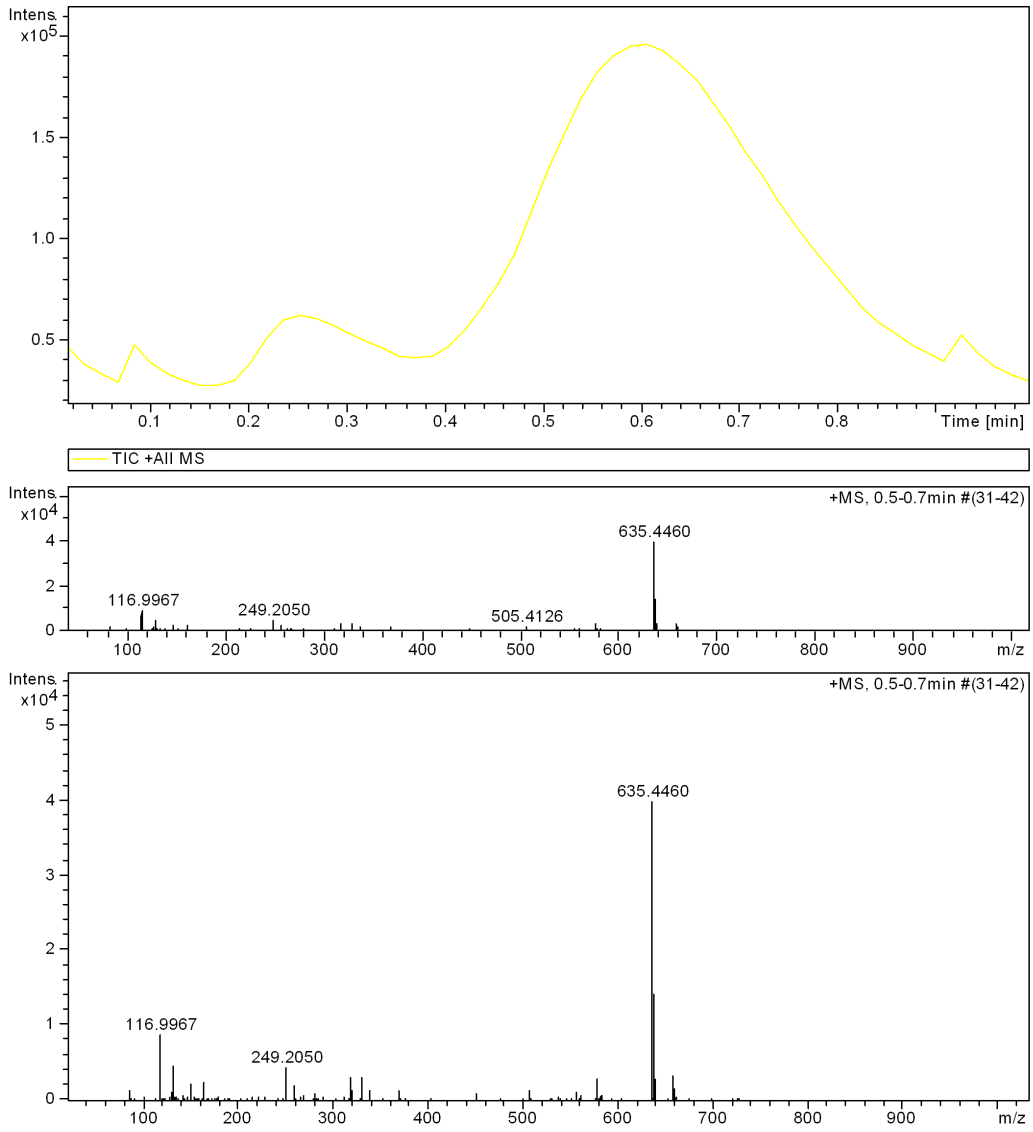
Analysis Name	D:\Data\Dogan\amer\RA-1-64.d	Acquisition Date	4/18/2019 9:16:38 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

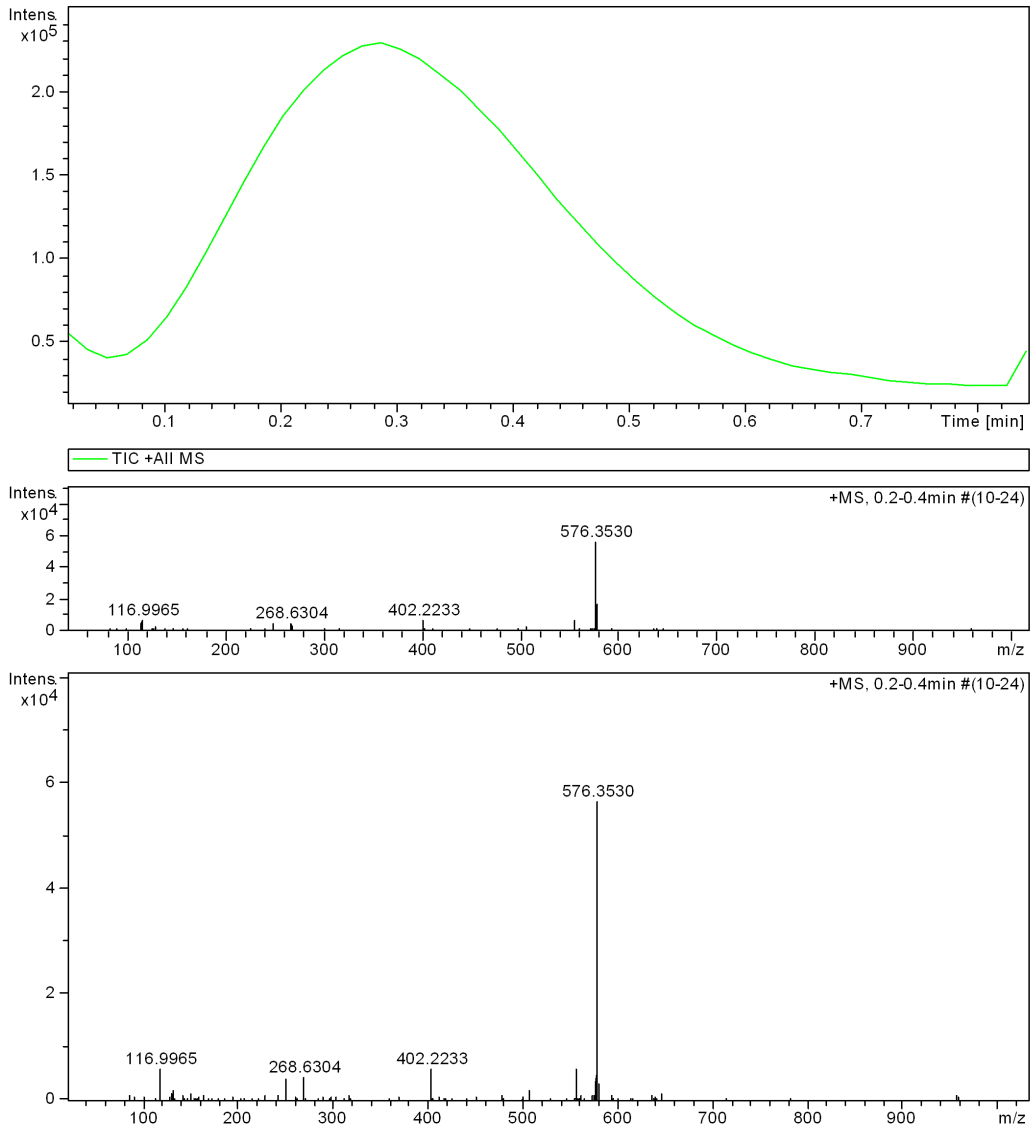
Analysis Name	D:\Data\Dogan\amer\RA-1-65-2.d	Acquisition Date	5/16/2019 3:11:08 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

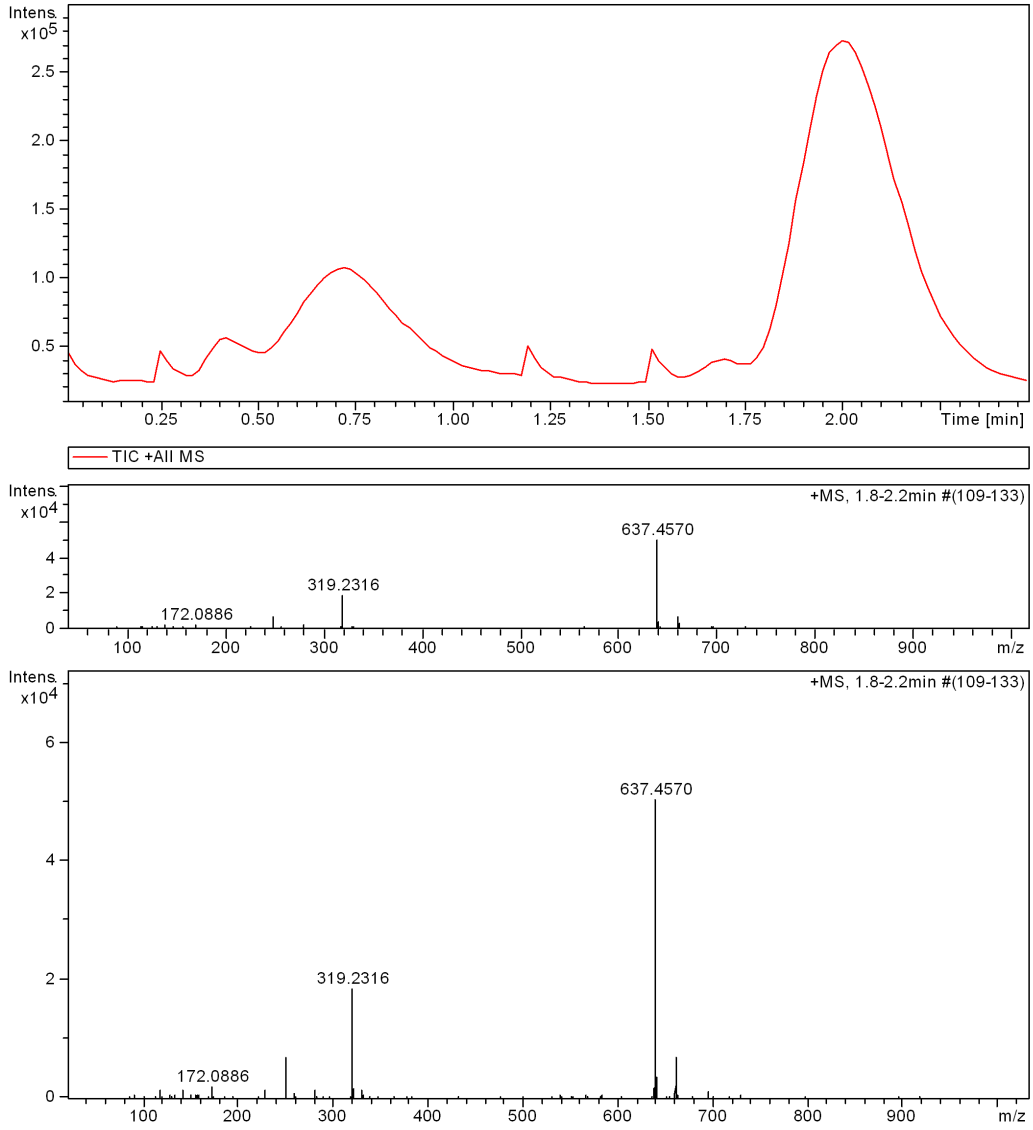
Analysis Name	D:\Data\Dogan\amer\RA-1-66.d	Acquisition Date	5/16/2019 3:05:07 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

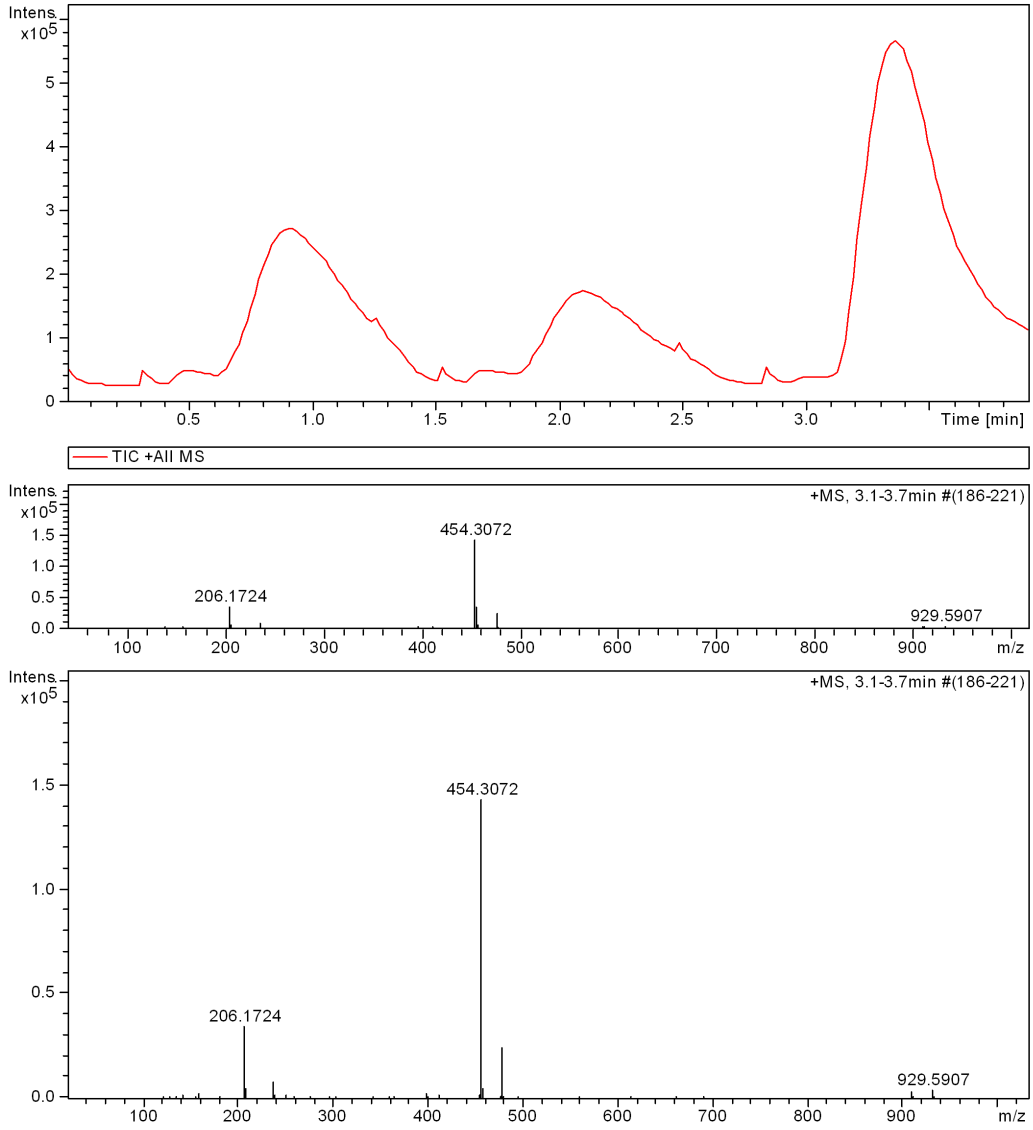
Analysis Name	D:\Data\Dogan\amer\RA-1-67.d	Acquisition Date	5/21/2019 2:35:33 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

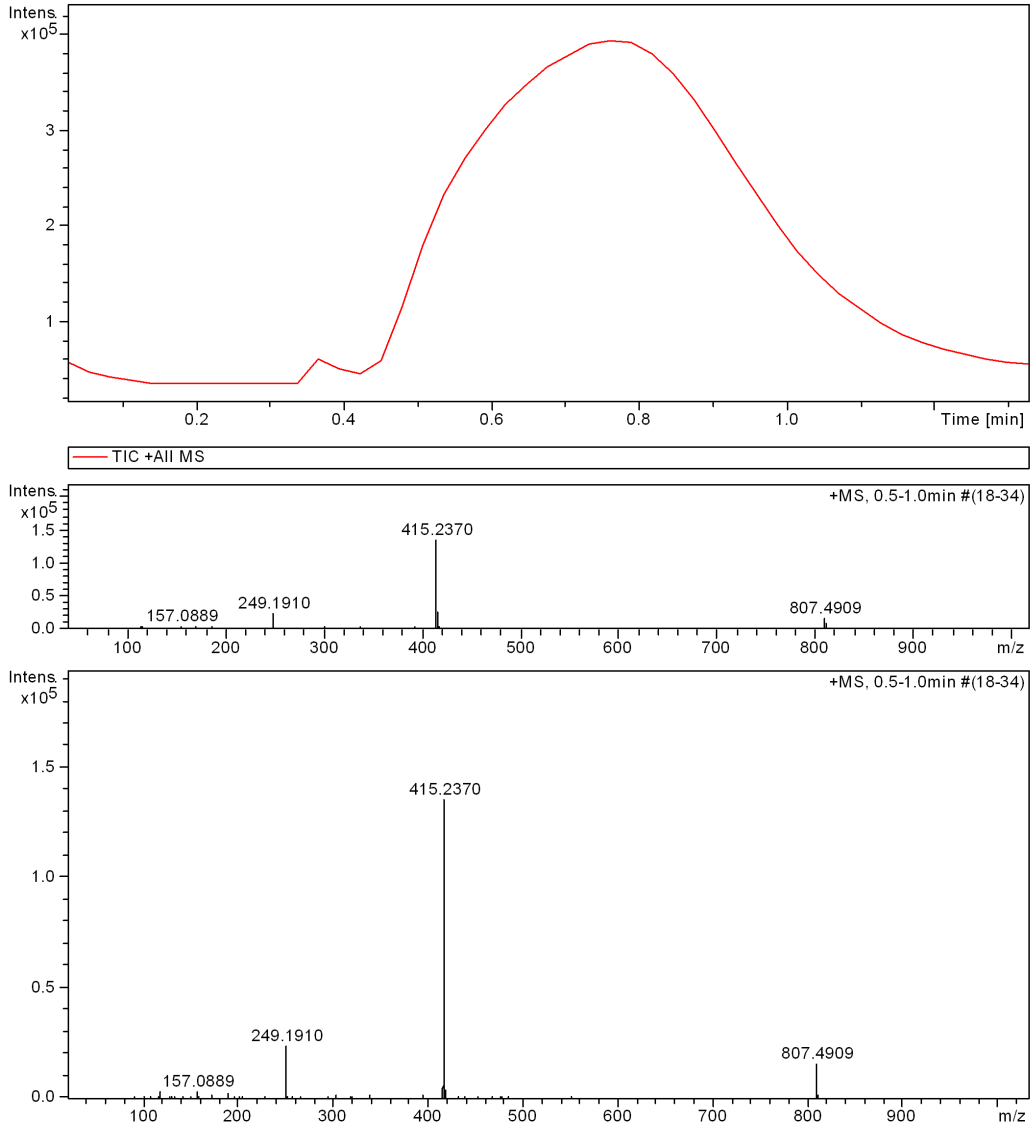
Analysis Name	D:\Data\Dogan\amer\RA-1-68.d	Acquisition Date	5/22/2019 1:36:25 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

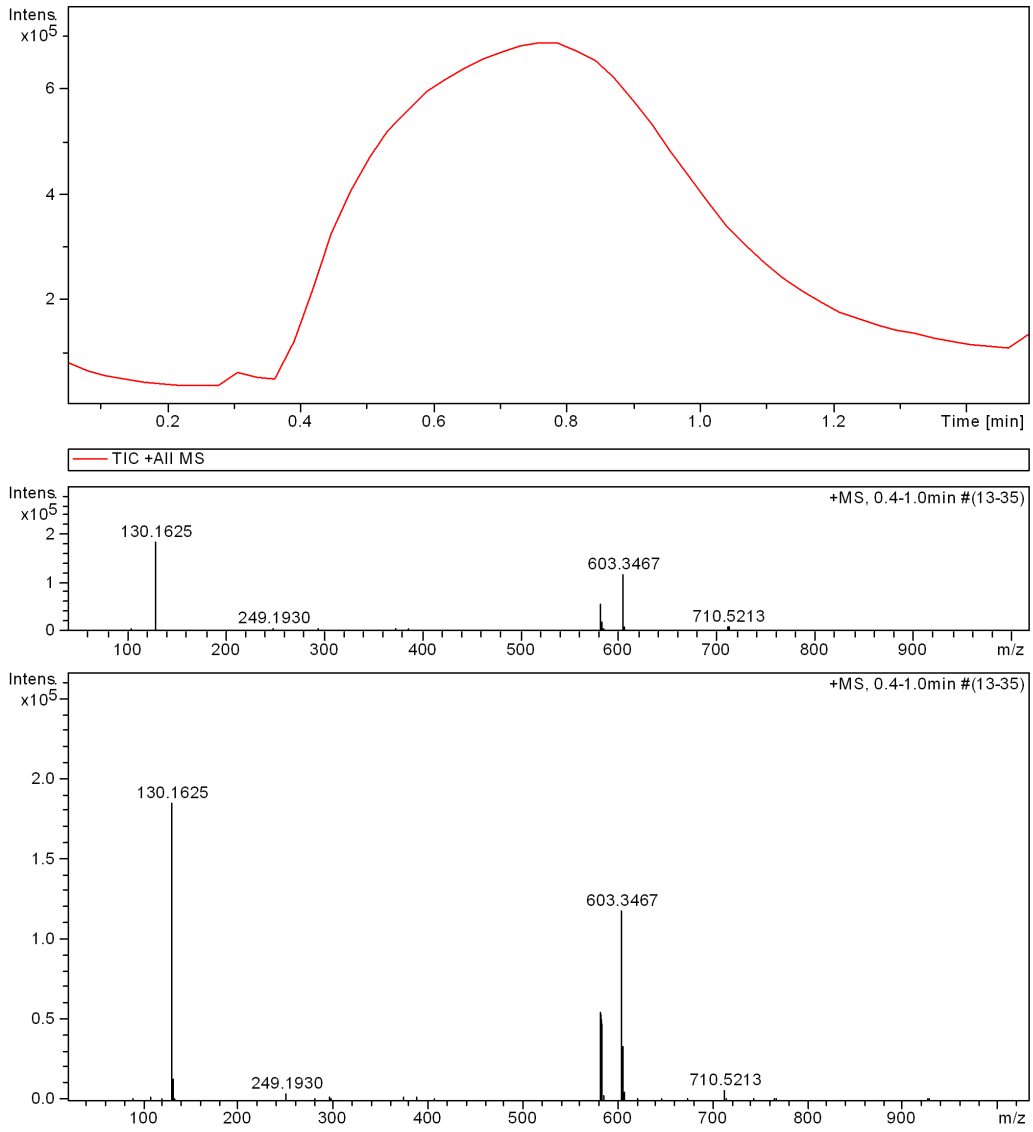
Analysis Name	D:\Data\Dogan\amer\RA-1-69.d	Acquisition Date	5/28/2019 10:03:58 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

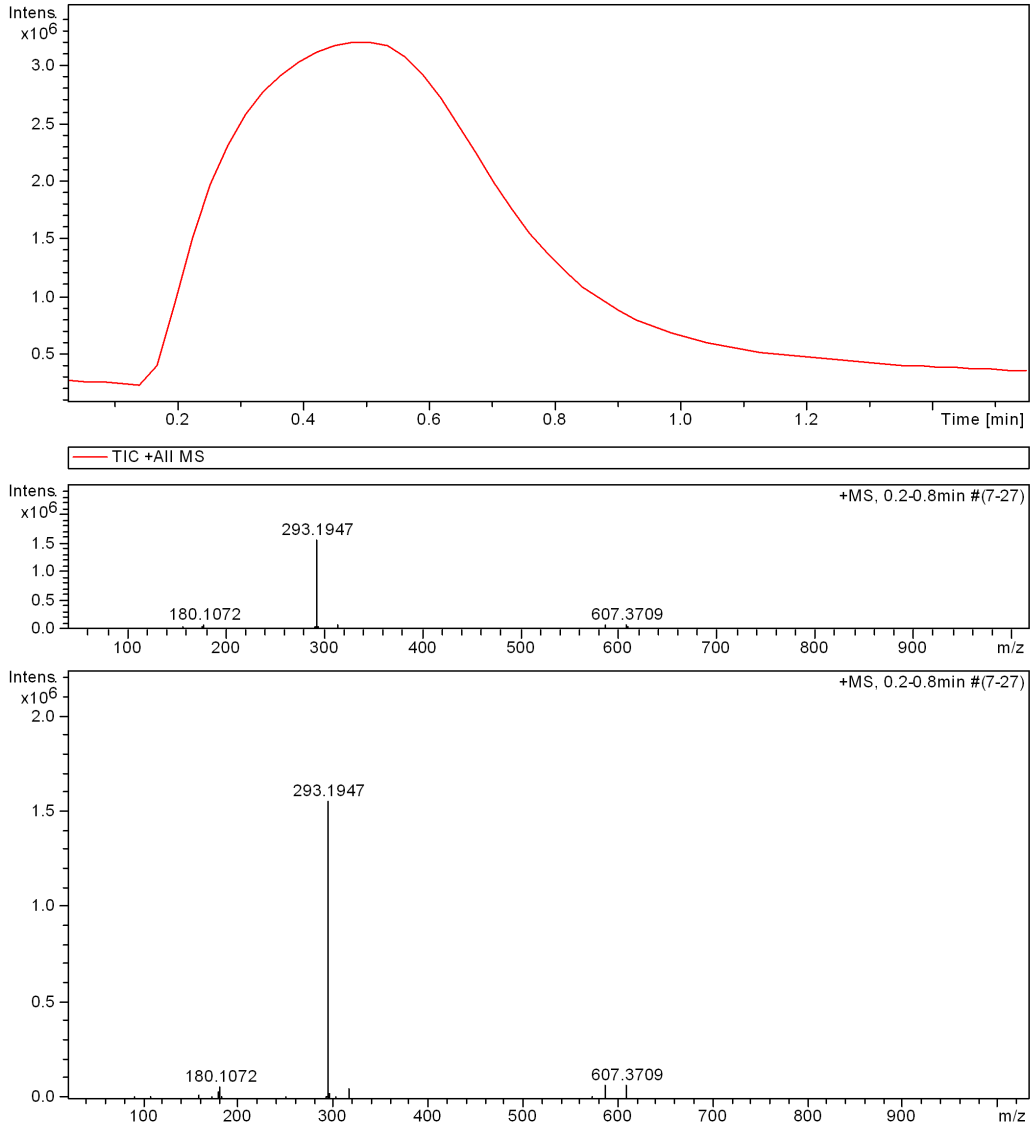
Analysis Name	D:\Data\Dogan\amer\RA-1-70.d	Acquisition Date	6/20/2019 12:39:08 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

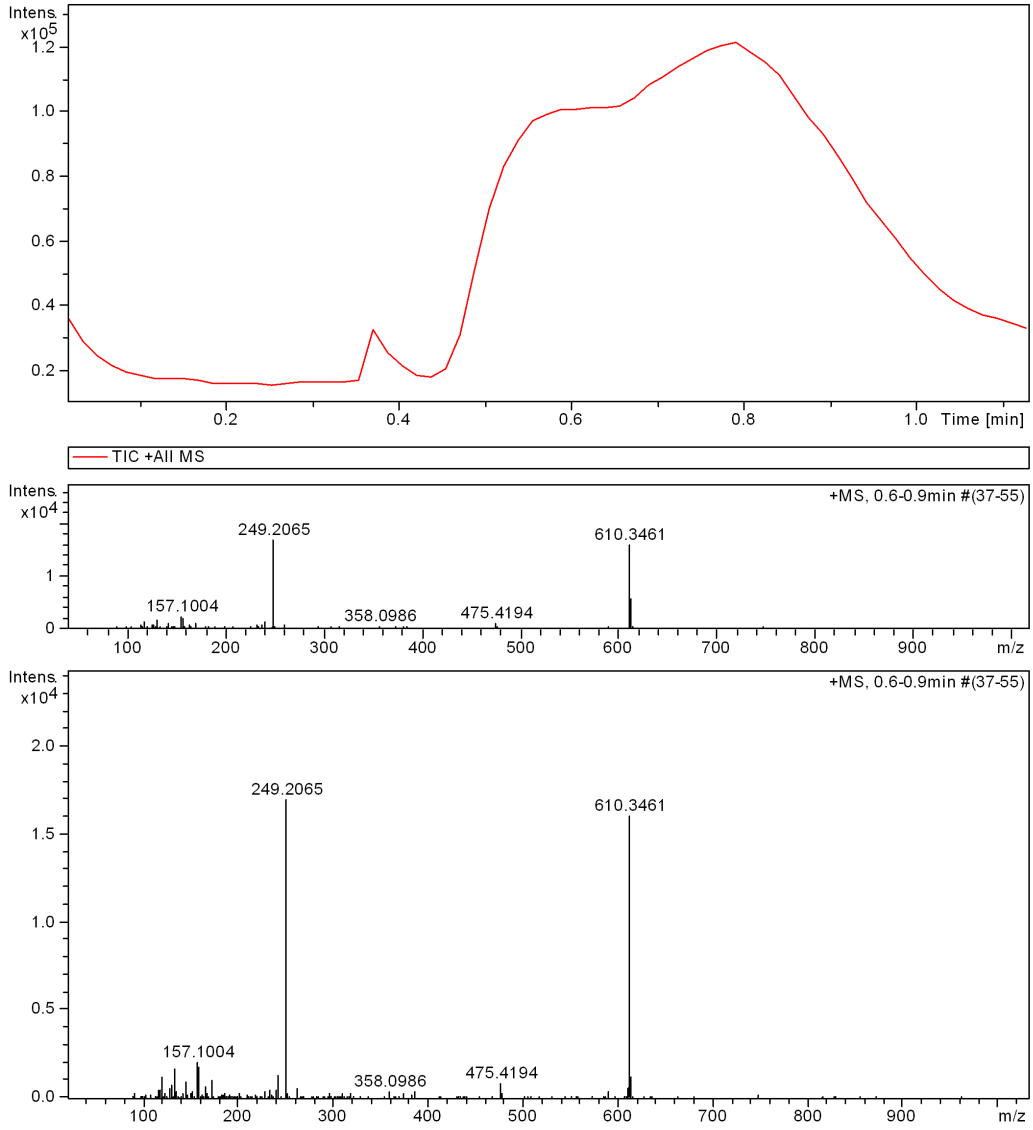
Analysis Name	D:\Data\Dogan\amer\RA-1-71.d	Acquisition Date	5/29/2019 11:50:34 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

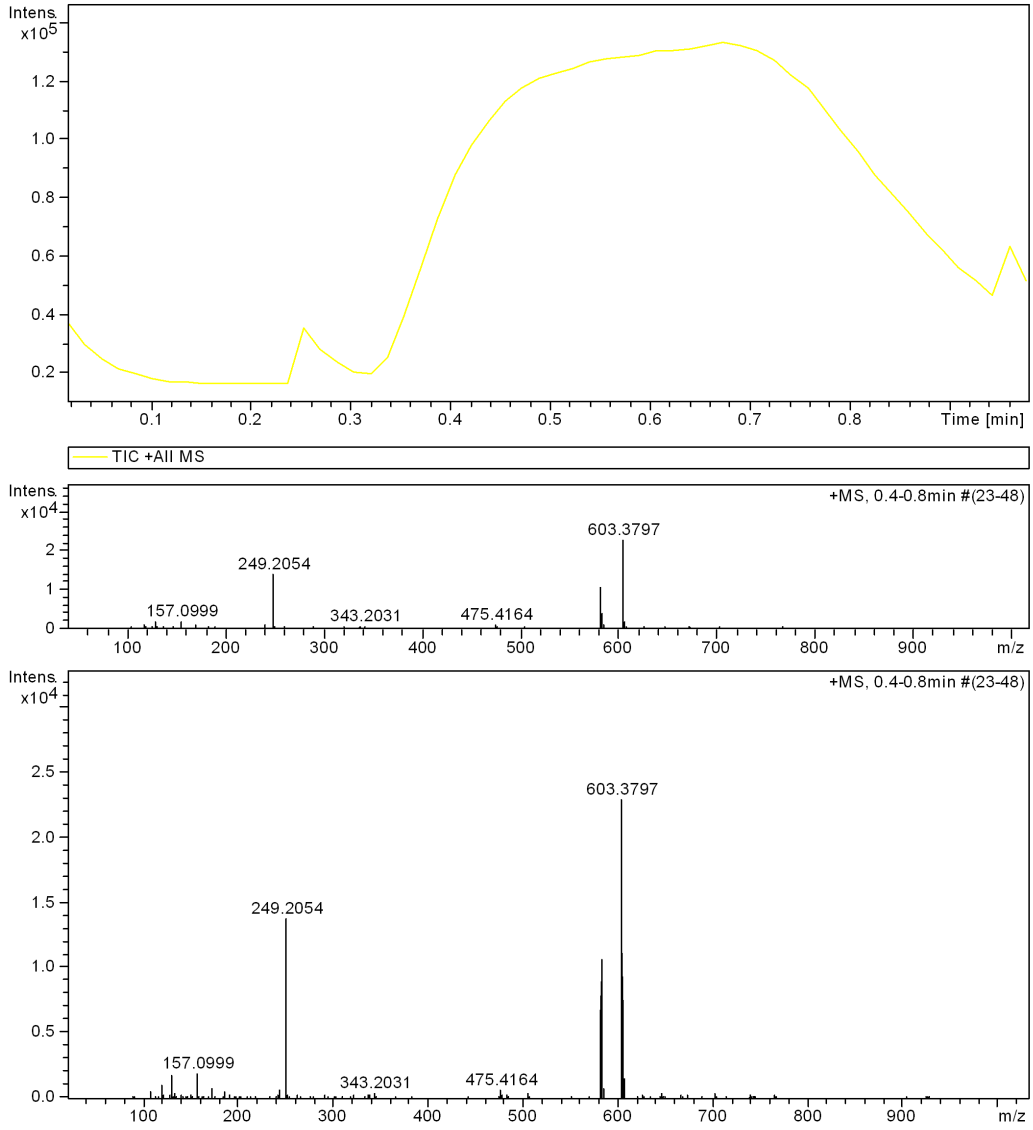
Analysis Name	D:\Data\Dogan\amer\RA-1-72.d	Acquisition Date	6/13/2019 9:50:42 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

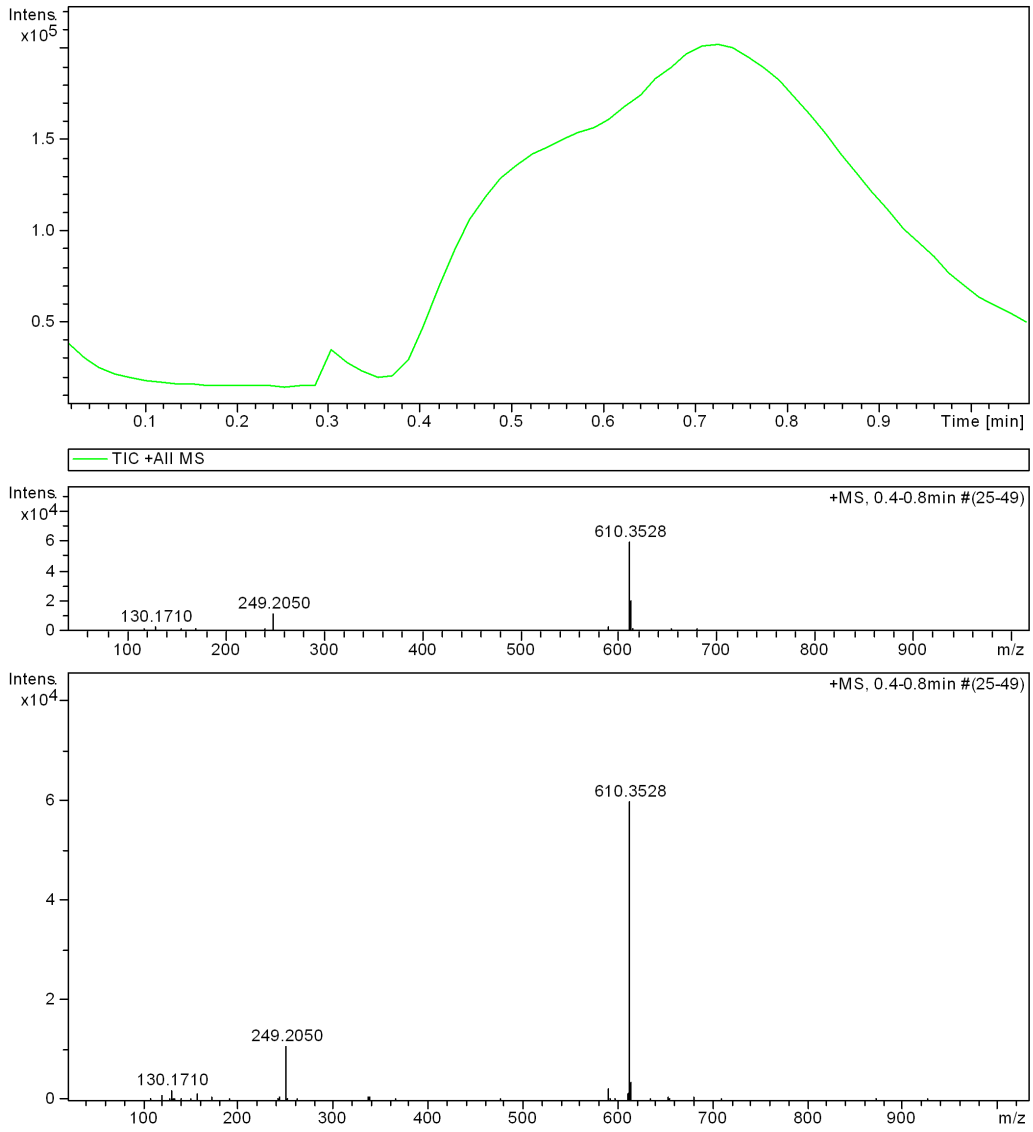
Analysis Name	D:\Data\Dogan\amer\RA-1-73-1.d	Acquisition Date	6/21/2019 1:45:03 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



Generic Display Report

Analysis Info

Analysis Name	D:\Data\Dogan\amer\RA-1-74-2.d	Acquisition Date	6/21/2019 1:40:51 PM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument	micrOTOF
Comment			



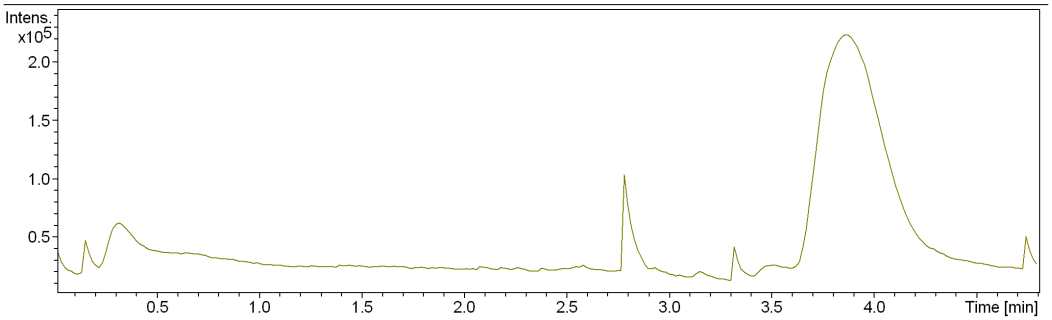
Display Report

Analysis Info

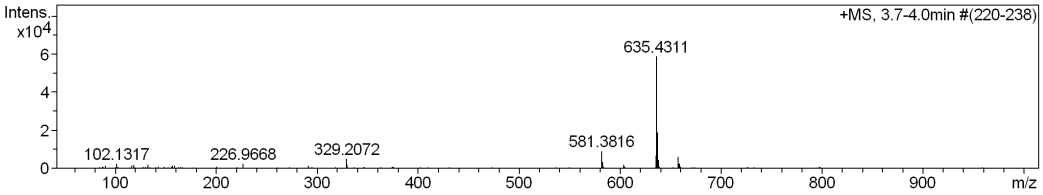
Analysis Name	D:\Data\Dogan\amer\RA-1-76-1.d	Acquisition Date	8/28/2019 11:40:29 AM
Method	Tune_Low.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

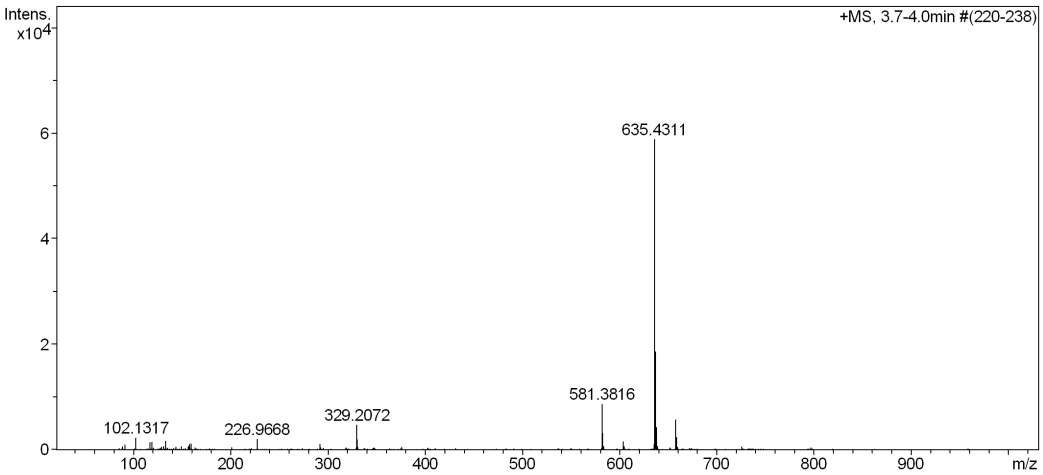
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



TIC +All MS





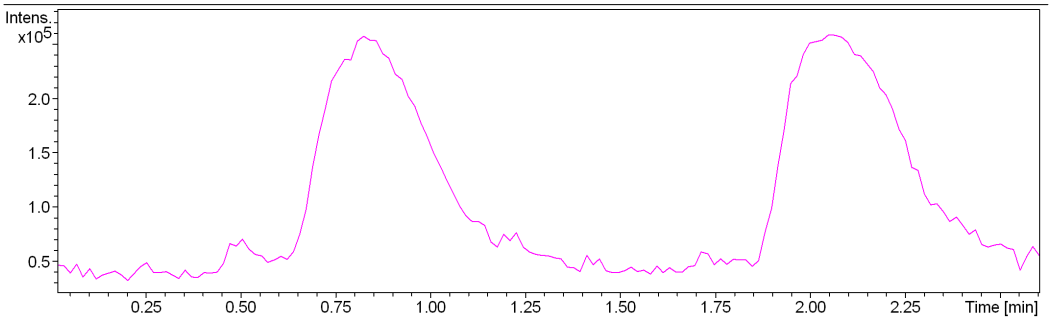
Display Report

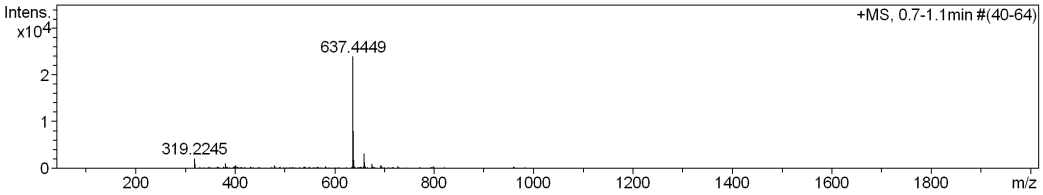
Analysis Info

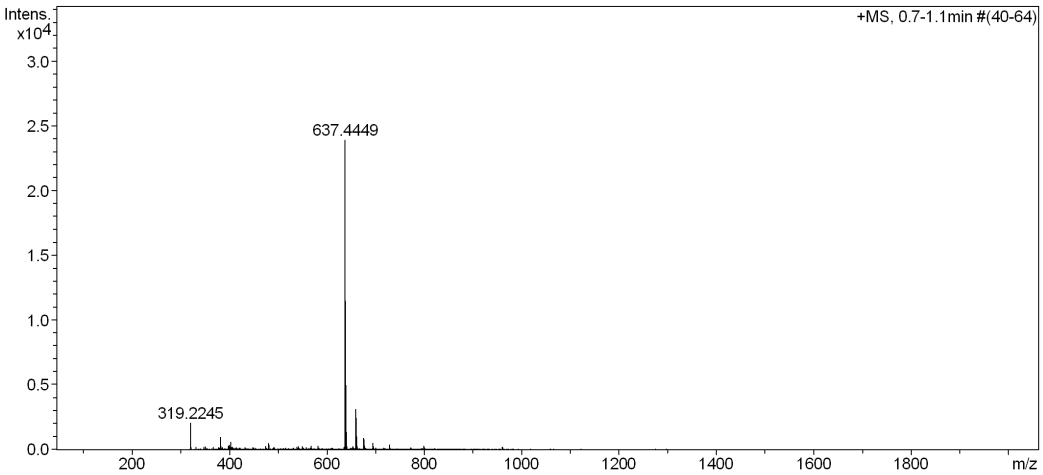
Analysis Name	D:\Data\Dogan\amer\RA-1-77.d	Acquisition Date	9/9/2019 12:09:34 PM
Method	Pos_Tuned for Masses in Mid Hundreds to 1000.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	50 m/z	Set Capillary	4500 V	Set Dry Gas	4.0 l/min
Scan End	2000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste







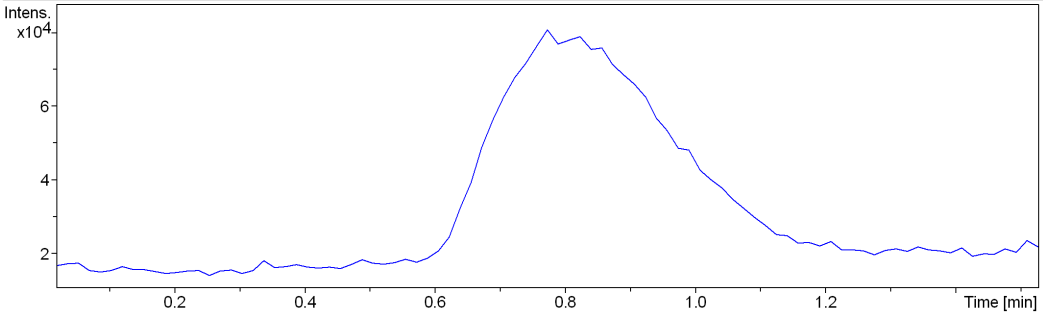
Display Report

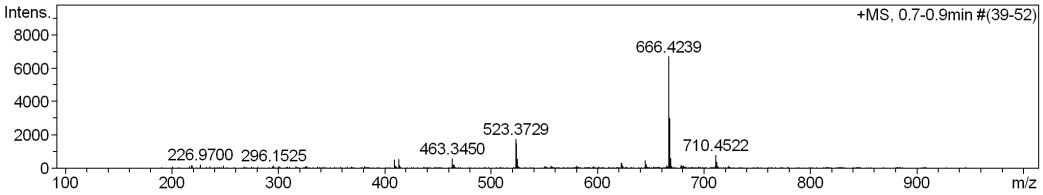
Analysis Info

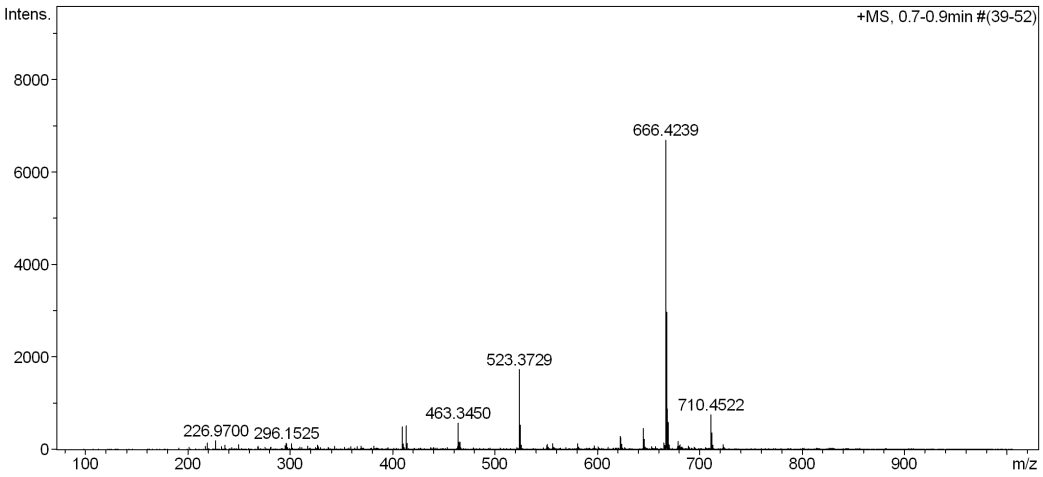
Analysis Name	D:\Data\Dogan\amer\RA-1-78-A.d	Acquisition Date	10/7/2019 11:08:16 AM
Method	Pos_Tuned for Masses in Mid Hundreds to 1000.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.5 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	100 m/z	Set Capillary	4800 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste







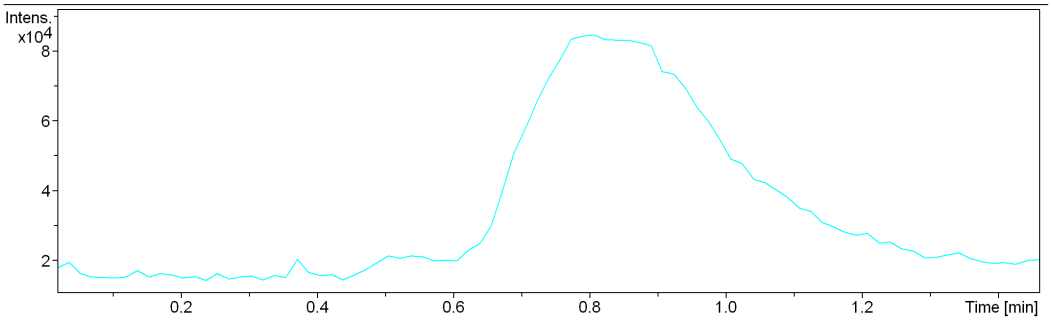
Display Report

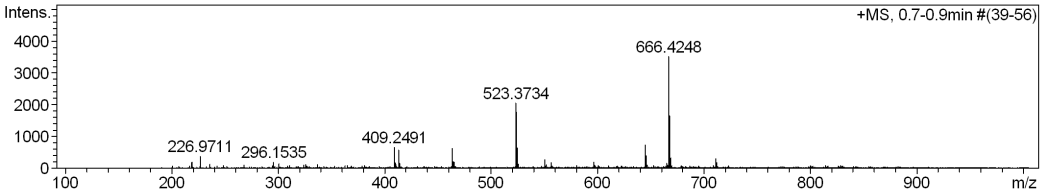
Analysis Info

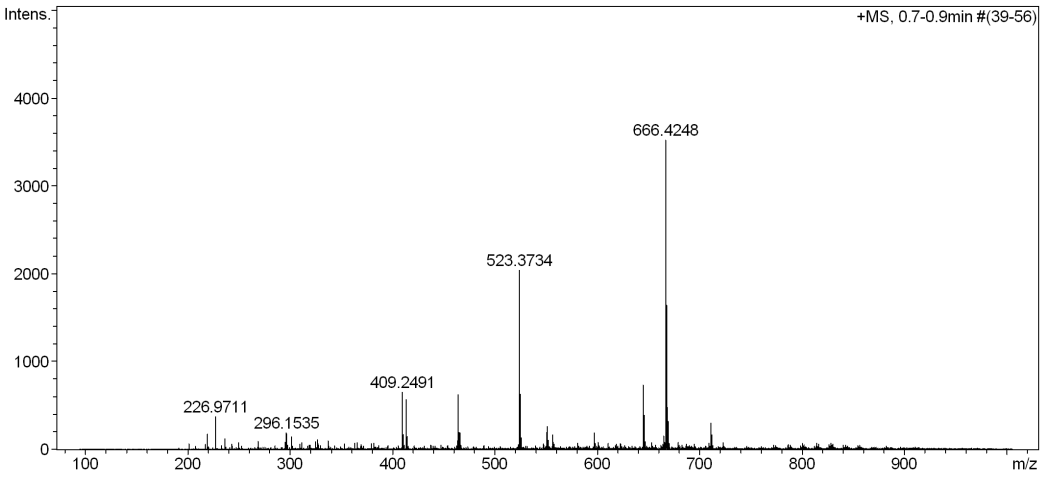
Analysis Name	D:\Data\Dogan\amer\RA-1-78-B.d	Acquisition Date	10/7/2019 11:01:11 AM
Method	Pos_Tuned for Masses in Mid Hundreds to 1000.m	Operator	amer.40
Sample Name		Instrument / Ser#	micrOTOF 194
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.5 Bar
Focus	Not active			Set Dry Heater	180 °C
Scan Begin	100 m/z	Set Capillary	4800 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



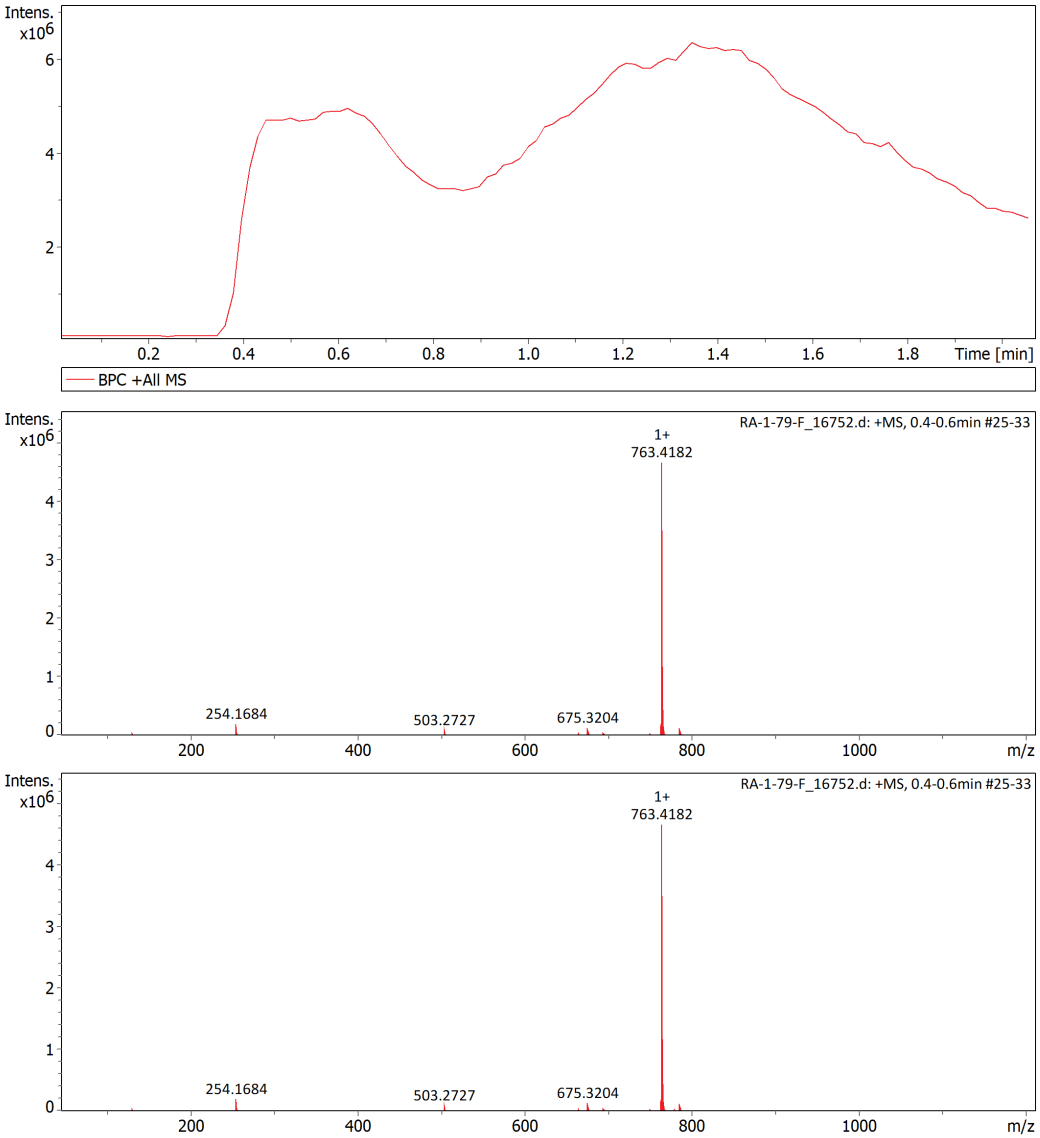




Generic Display Report

Analysis Info

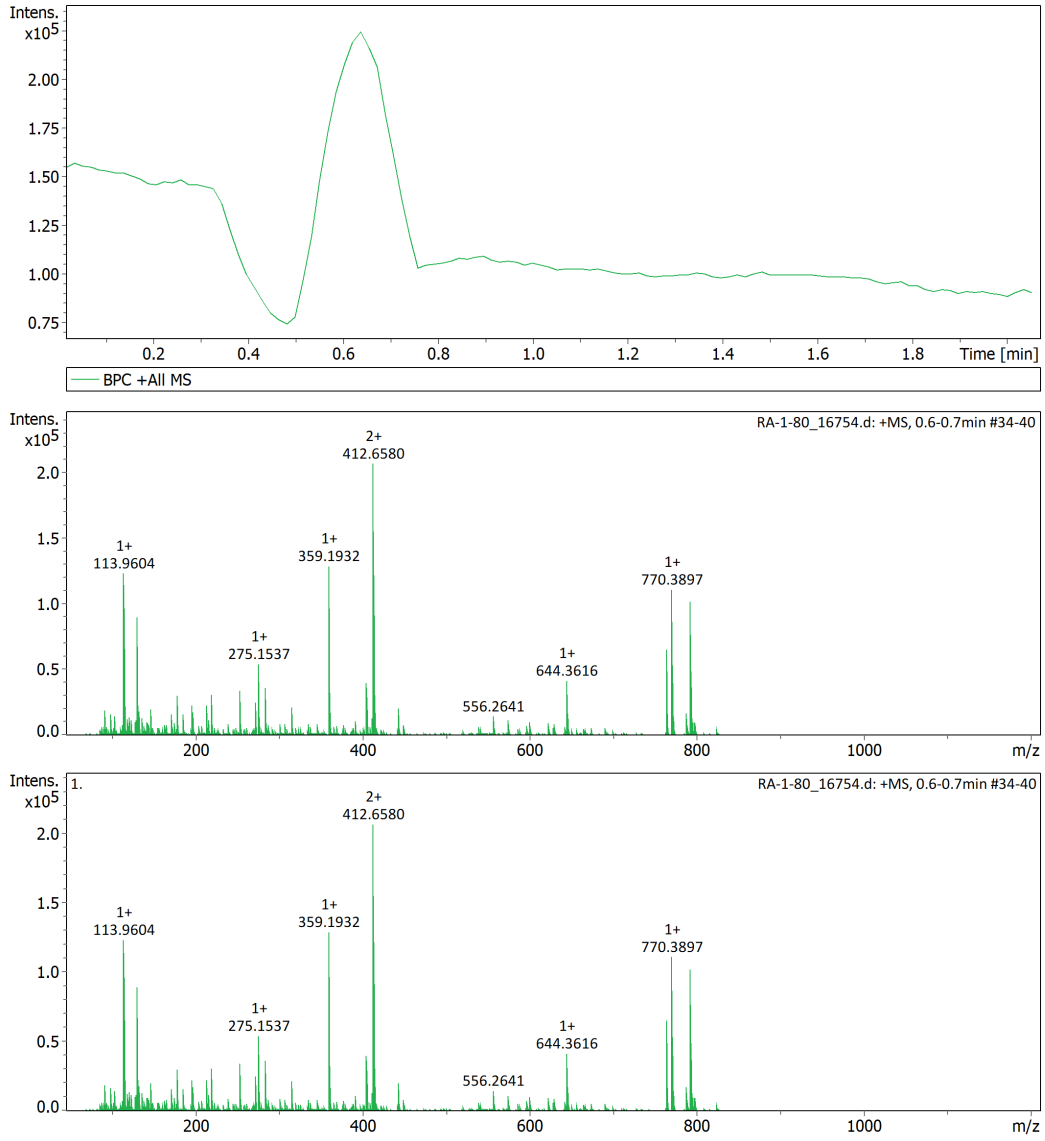
Analysis Name	X:\Ozlem Dogan Ekici\Amer.40\11.16.21\RA-1-79-F_16752.d	Acquisition Date	11/16/2021 9:41:54 AM
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-79-F	Instrument	impact II
Comment			



Generic Display Report

Analysis Info

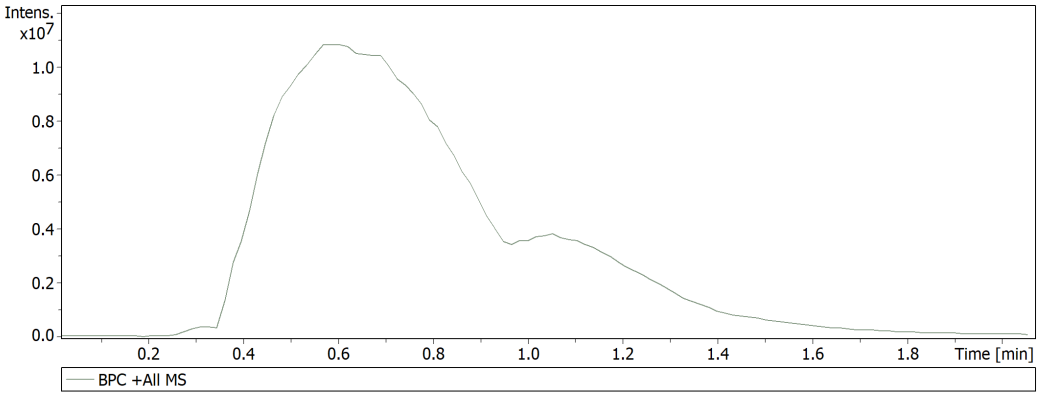
Analysis Name	X:\Ozlem Dogan Ekici\Amer.40\11.16.21\RA-1-80_16754.d	Acquisition Date	11/16/2021 9:48:22 AM
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-80	Instrument	impact II
Comment			

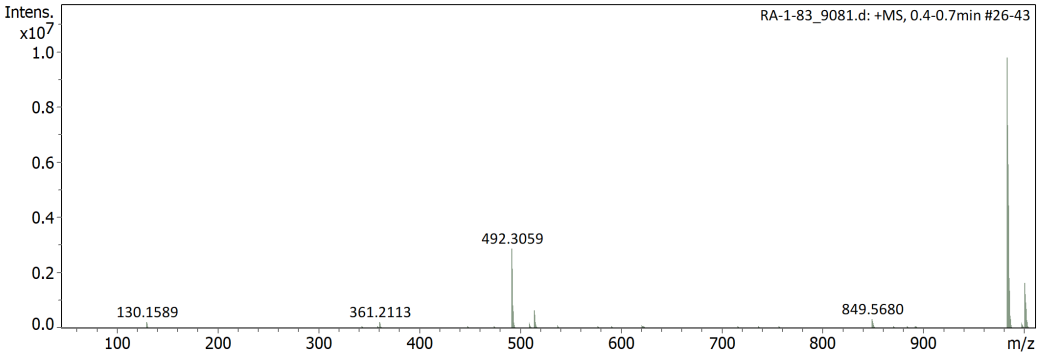


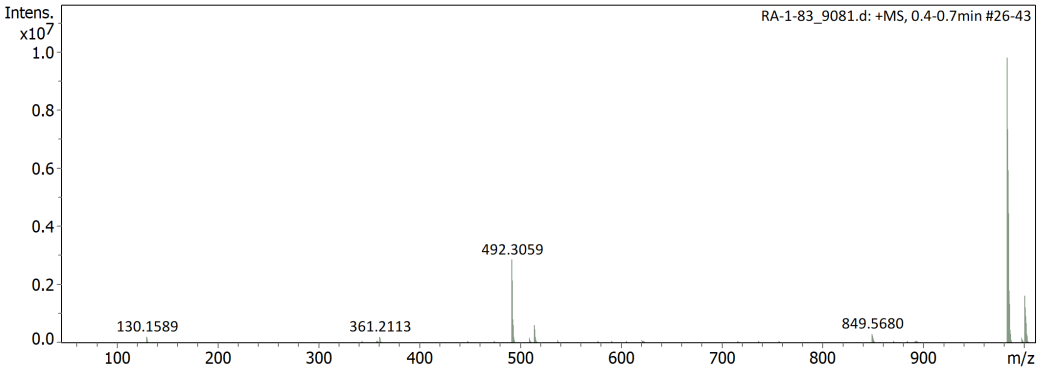
Generic Display Report

Analysis Info

Analysis Name	X:\Ozlem Dogan Ekici\Amer.40\2021\3.9.21\RA-1-83_9081.d	Acquisition Date	3/9/2021 2:34:03 PM
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-83	Instrument	impact II
Comment			



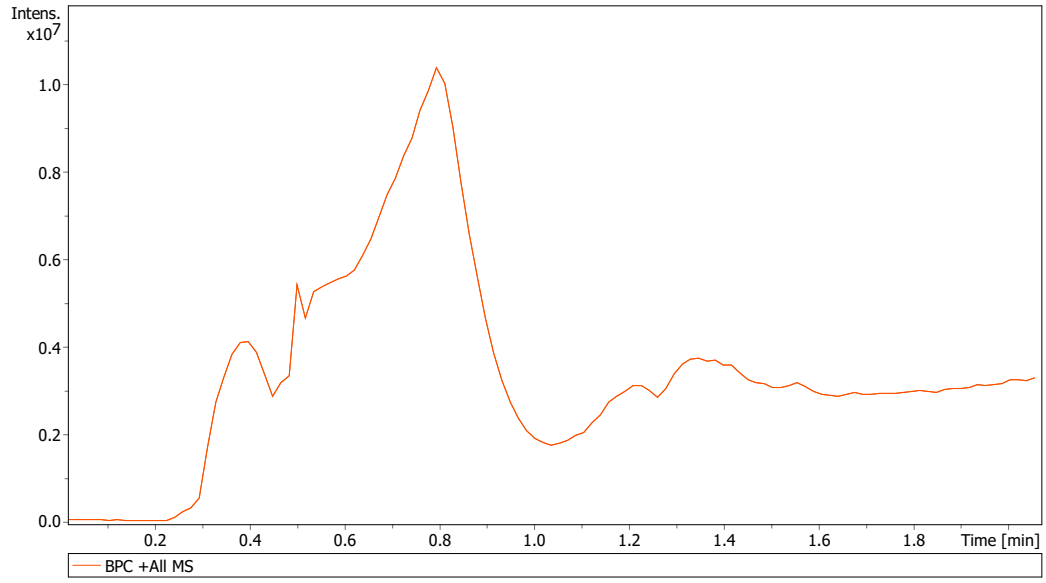


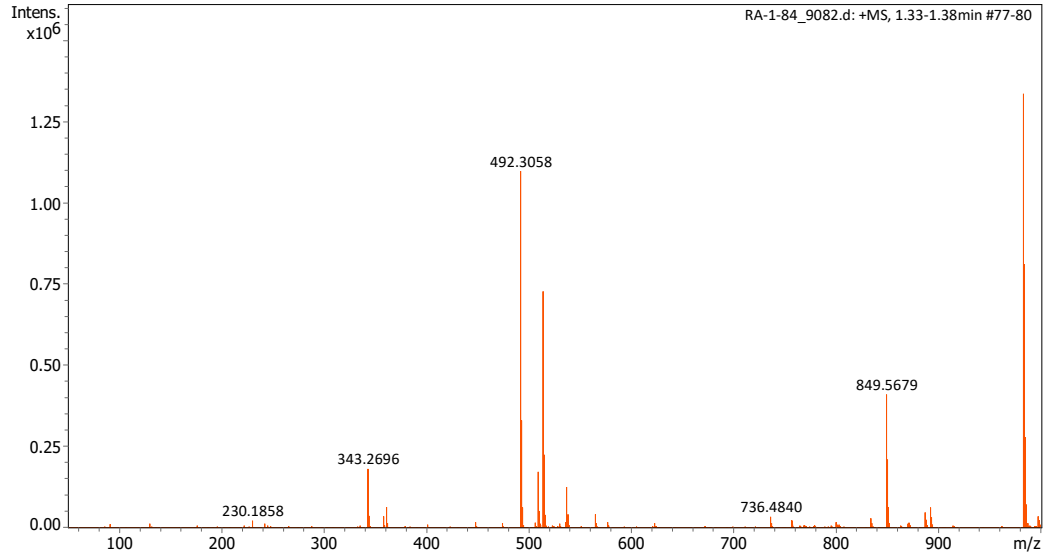


Generic Display Report

Analysis Info

Analysis Name	Z:\Ozlem Dogan Ekici\Amer.40\RA-1-84_9082.d	Acquisition Date	3/9/2021 2:36:35 PM
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-84	Instrument	impact II
Comment			

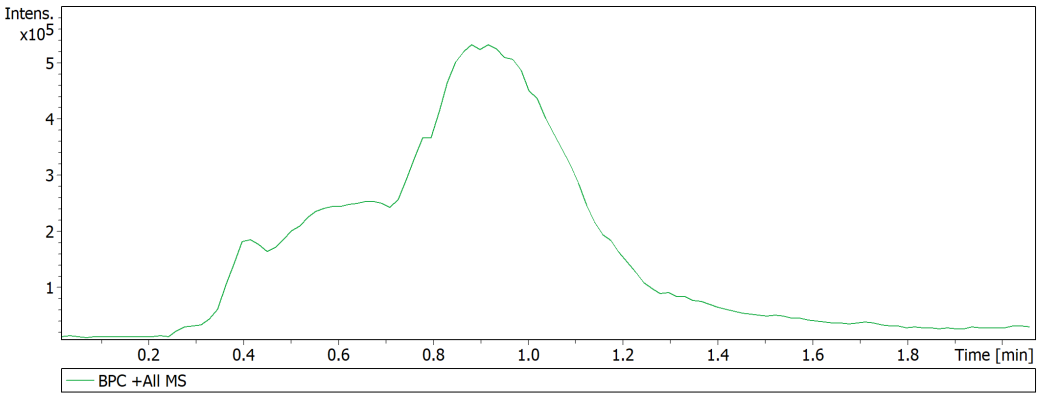


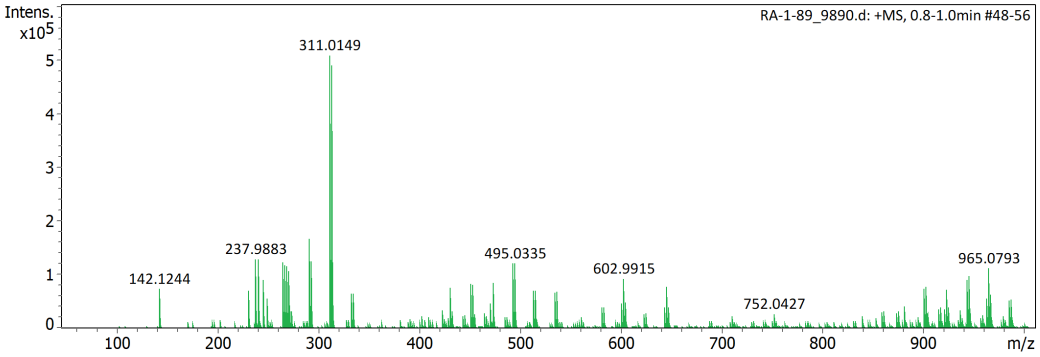


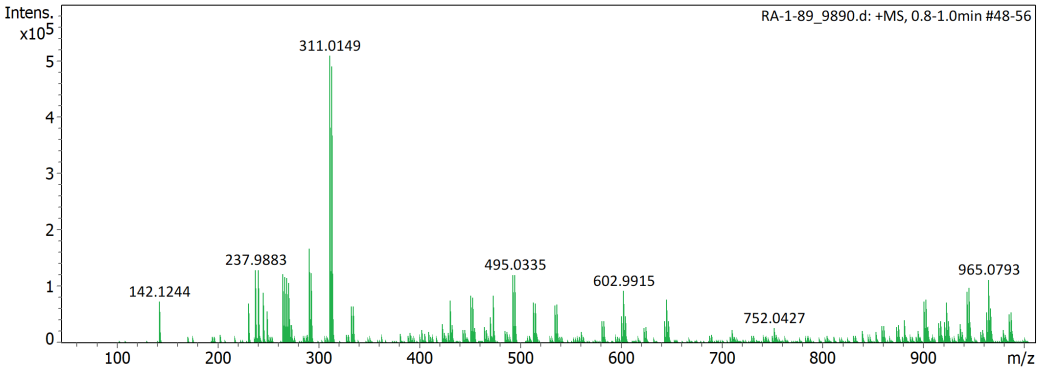
Generic Display Report

Analysis Info

Analysis Name	X:\Ozlem Dogan Ekici\Amer.40\2021\3.30.21\RA-1-89_9890.d	Acquisition Date	3/30/2021 1:17:00 PM
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-89	Instrument	impact II
Comment			



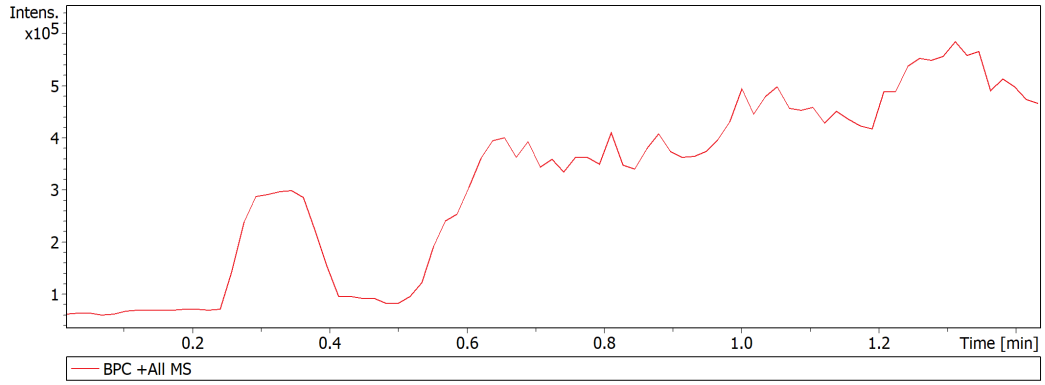


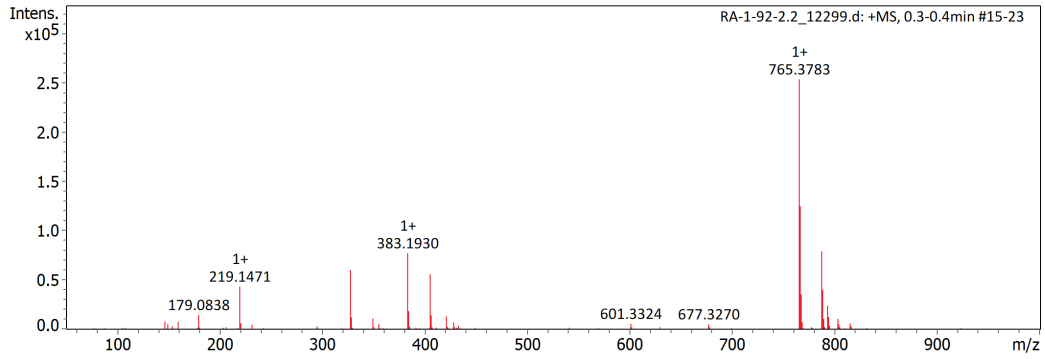


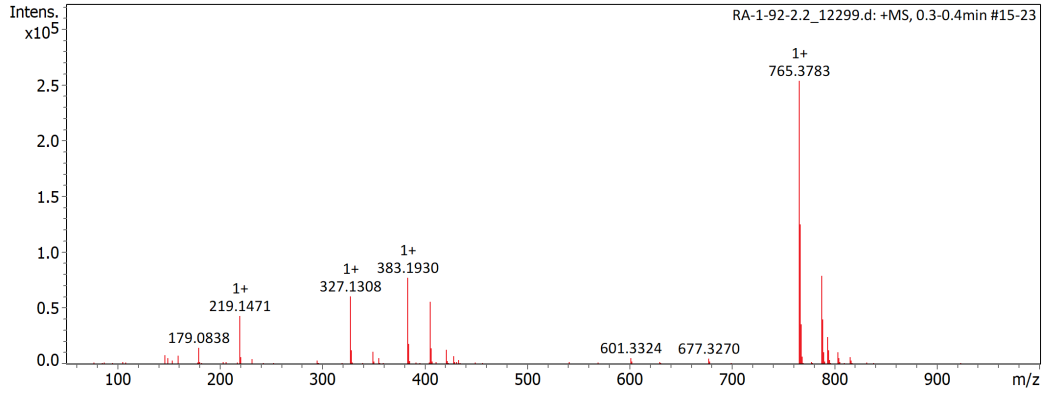
Generic Display Report

Analysis Info

Acquisition Date	6/16/2021 3:26:01 PM		
Analysis Name	\\files\cbc\Research-NB\Mass Spec\Impact ESI\Ozlem Dogan Ekici\Amer.40\6.16.21\RA-1-92-2.2_12299.d		
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-92-2.2	Instrument	impact II
Comment			



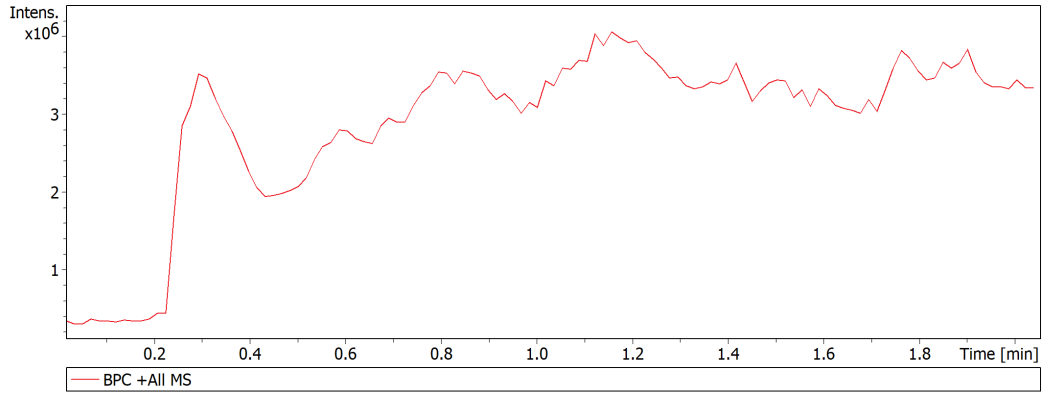


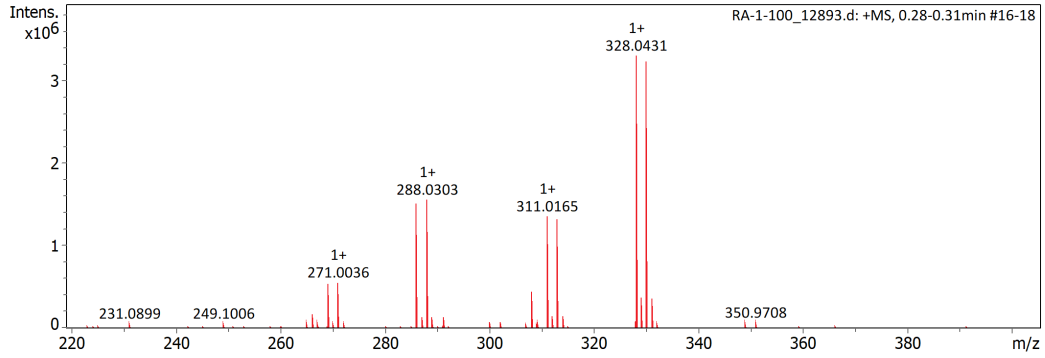


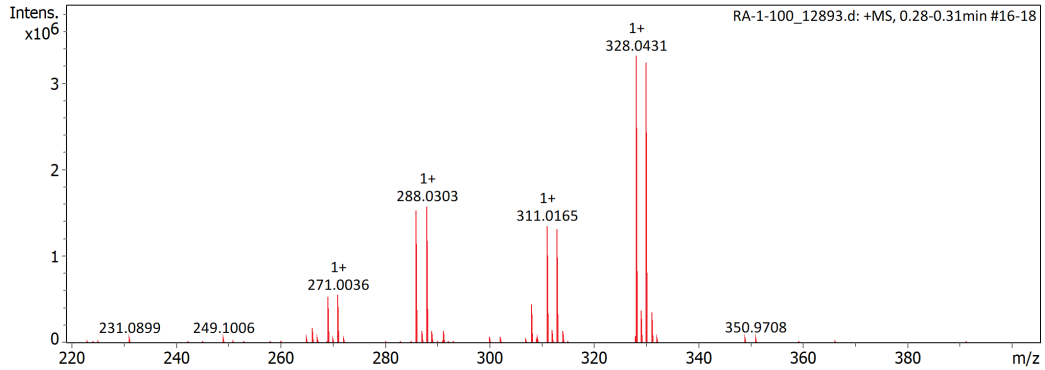
Generic Display Report

Analysis Info

Acquisition Date	6/24/2021 7:36:02 PM		
Analysis Name	\\files\cbc\Research-NB\Mass Spec\Impact ESI\Ozlem Dogan Ekici\Amer.40\6.24.21\RA-1-100_12893.d		
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-100	Instrument	impact II
Comment			



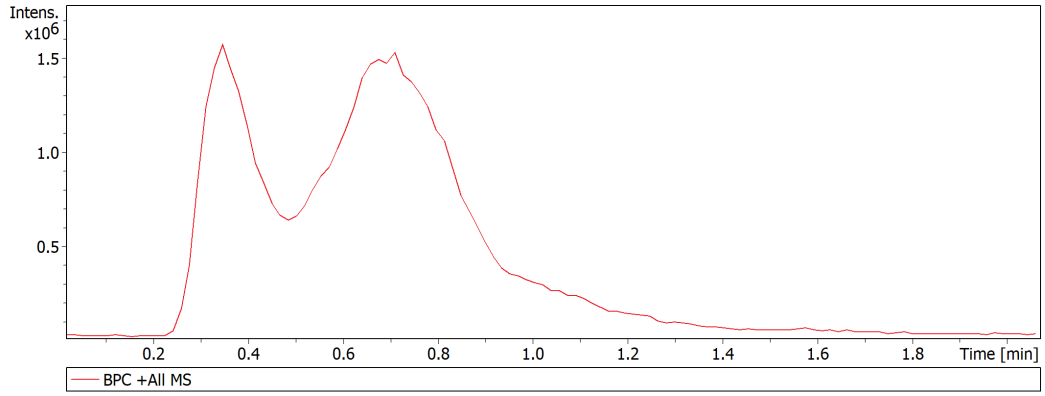


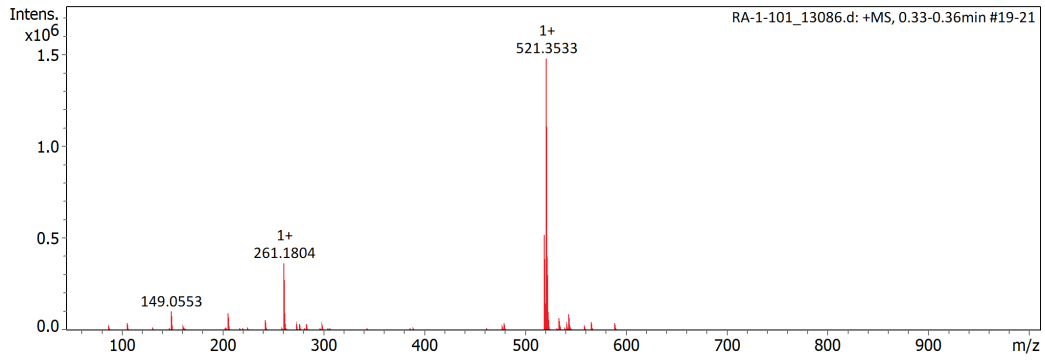


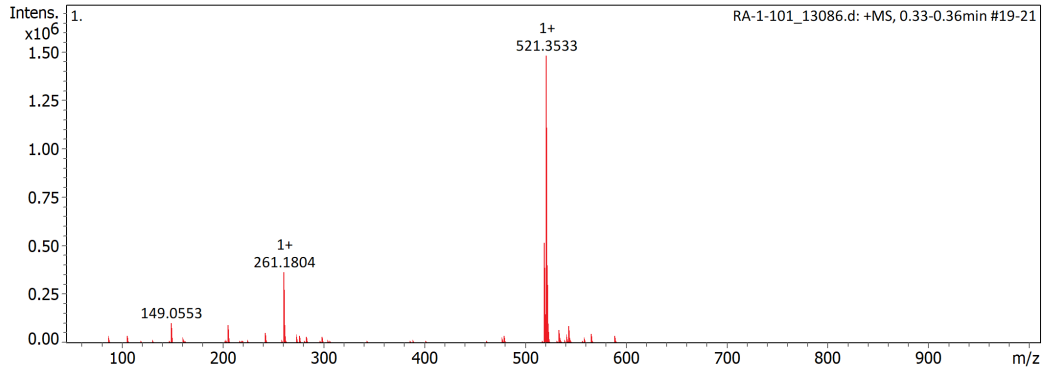
Generic Display Report

Analysis Info

Acquisition Date	7/1/2021 2:16:50 PM		
Analysis Name	\\files\cbc\Research-NB\Mass Spec\Impact ESI\Ozlem Dogan Ekici\Amer.40\7.1.21\RA-1-101_13086.d		
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-101	Instrument	impact II
Comment			



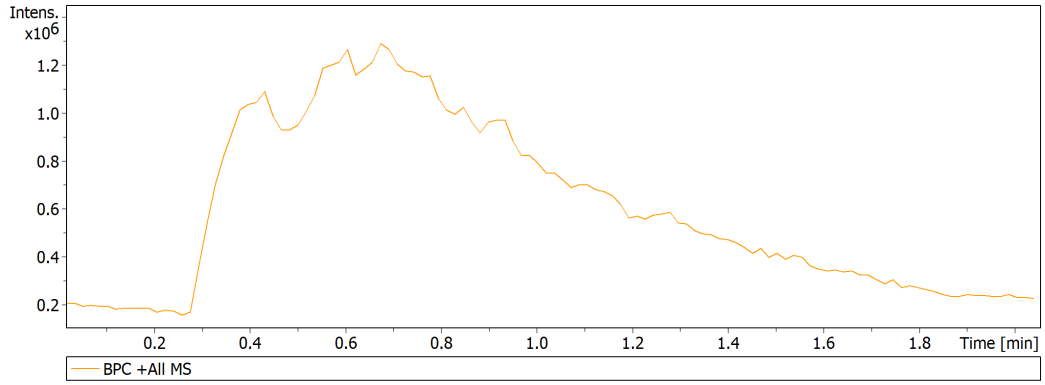


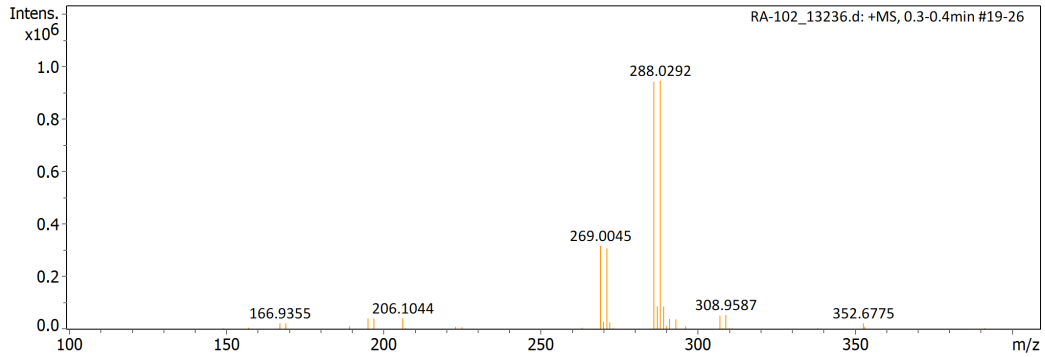


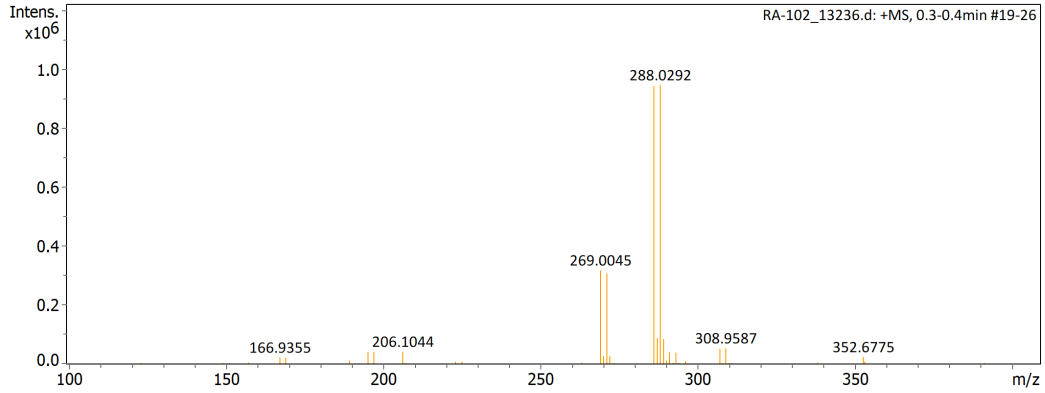
Generic Display Report

Analysis Info

Acquisition Date	7/13/2021 8:52:19 AM		
Analysis Name	\\files\cbc\Research-NB\Mass Spec\Impact ESI\Ozlem Dogan Ekici\Amer.40\7.13.21\RA-102_13236.d		
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-102	Instrument	impact II
Comment			



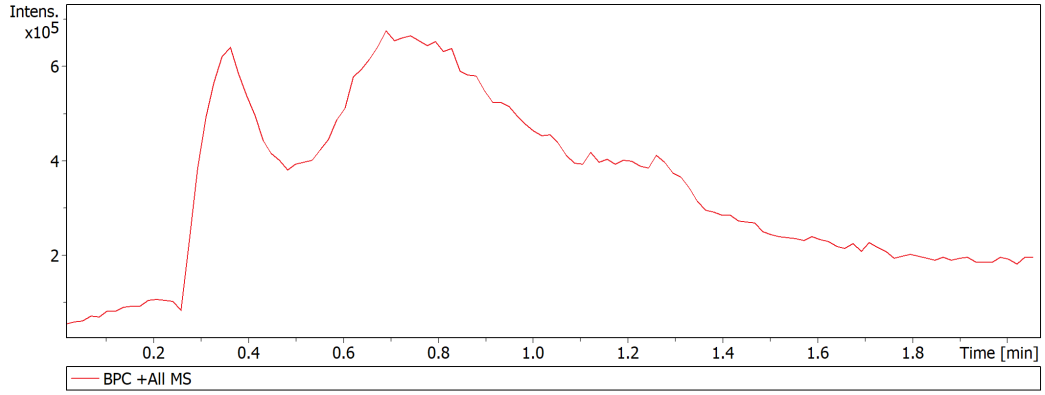


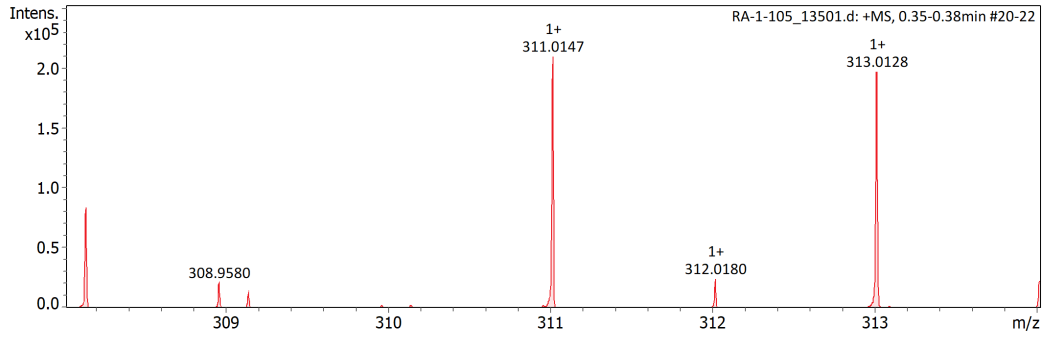


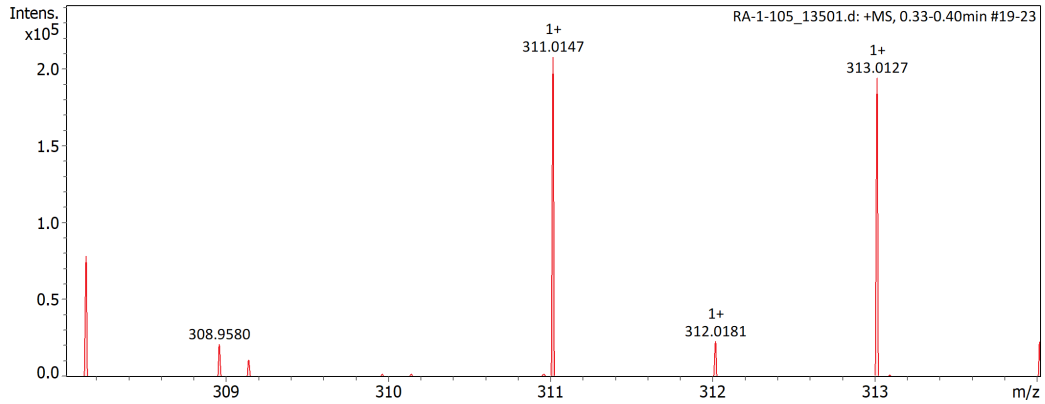
Generic Display Report

Analysis Info

		Acquisition Date	7/21/2021 2:24:34 PM
Analysis Name	X:\Ozlem Dogan Ekici\Amer.40\2021\7.21.21\RA-1-105_13501.d		
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-105	Instrument	impact II
Comment			

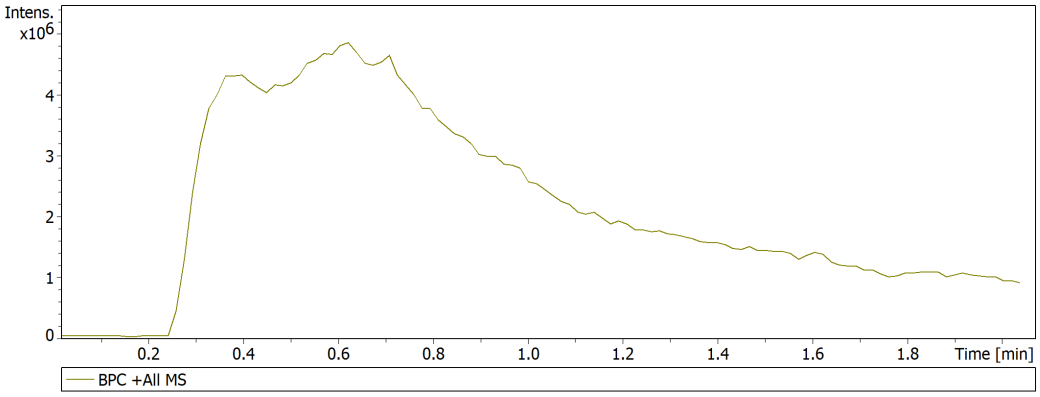


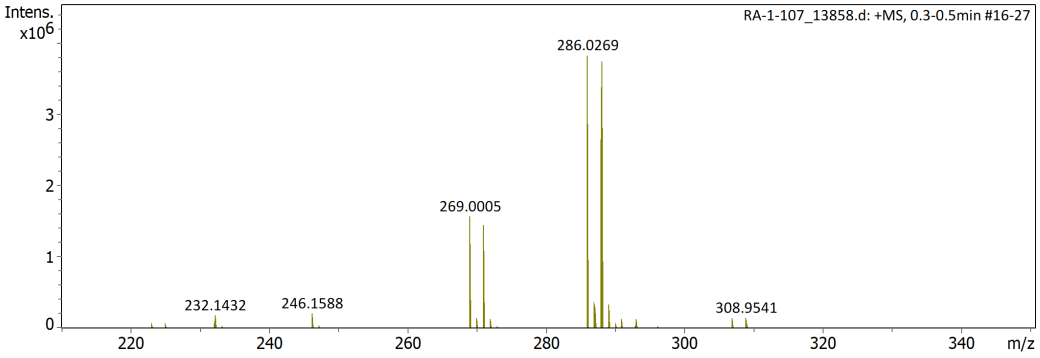


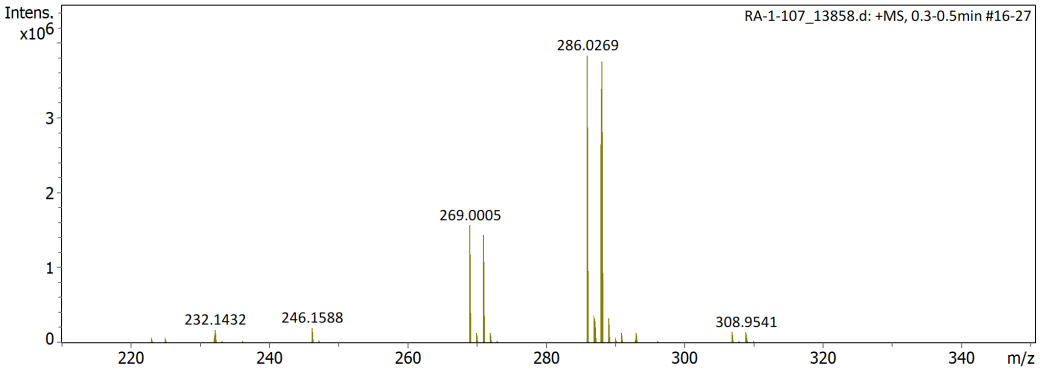


Generic Display Report

Analysis Info			
Analysis Name	X:\Ozlem Dogan Ekici\Amer.40\2021\7.28.21\RA-1-107_13858.d	Acquisition Date	7/29/2021 12:05:43 PM
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-107	Instrument	impact II
Comment			







Generic Display Report

Analysis Info

Analysis Name	X:\Ozlem Dogan Ekici\Amer.40\10.15.21\RA-1-113_16102.d	Acquisition Date	10/15/2021 10:57:57 AM
Method	Autosampler Tune Low.m	Operator	CBC Mass Spec Facility
Sample Name	RA-1-113	Instrument	impact II
Comment